

AMERICAN JOURNAL OF OPHTHALMOLOGY

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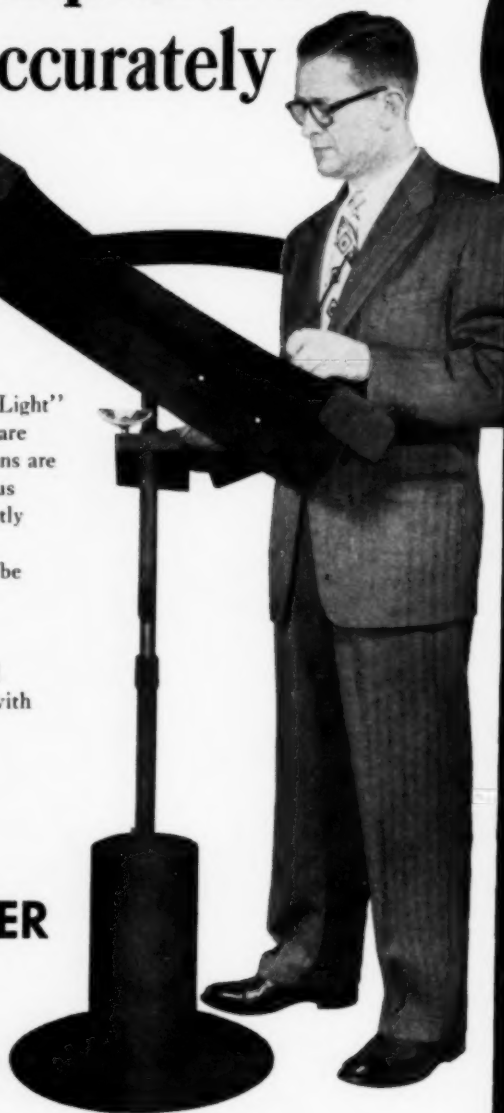
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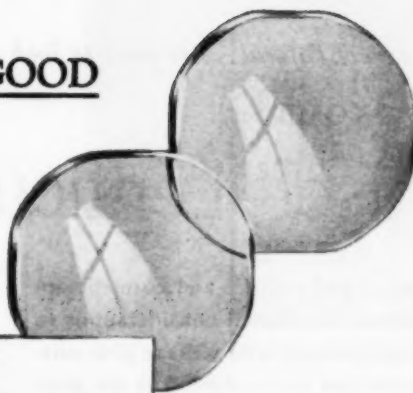
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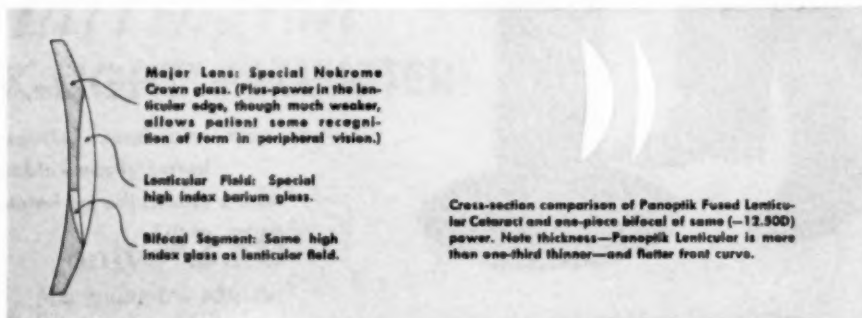
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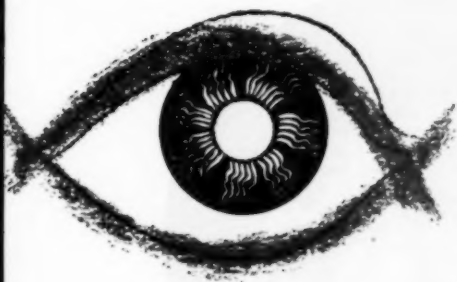
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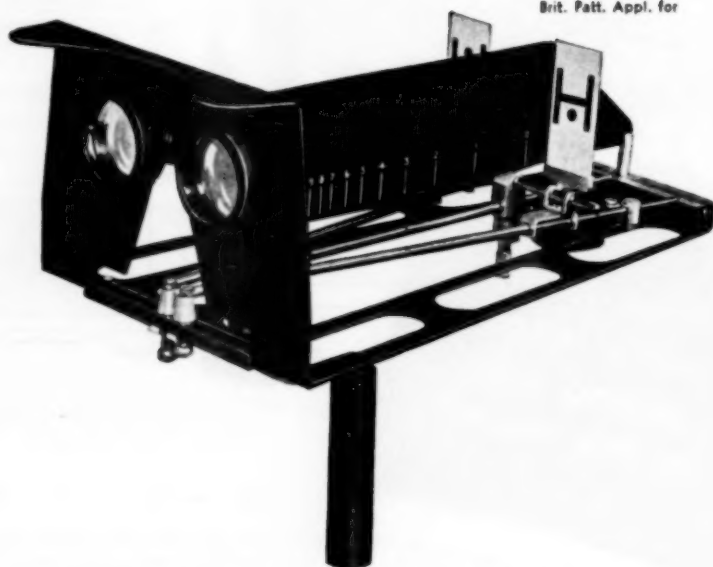
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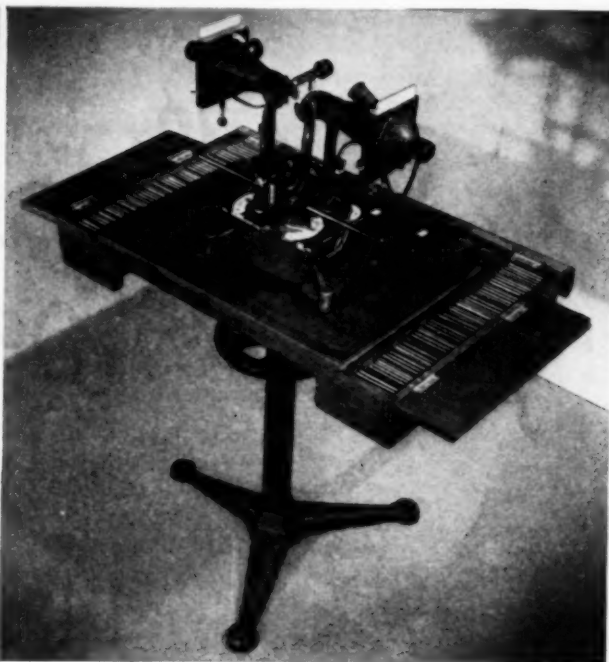
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1. Gotes, B. C., and Leopold, I. H.: *Arch. of Ophth.* 40:54 (Jan.) 1953

2. Seidner, I. H.: *Am. J. Ophth.* (Jan.) 1953

3. Pritchard, R. K., and McIlroy, M. N.: *Am. J. Ophth.* 34:572 (April) 1952

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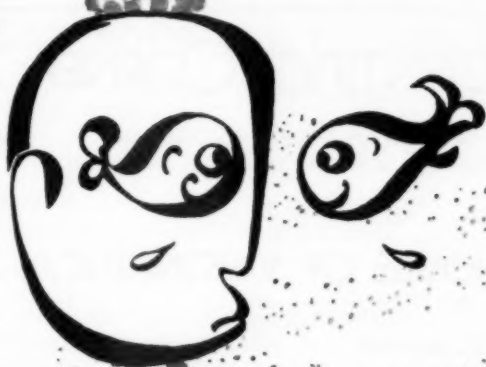
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PRISM MEASUREMENT

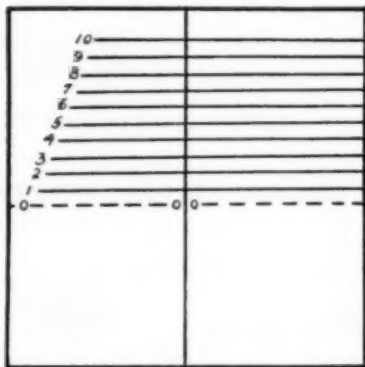
In the April Scientific Corner, we presented the calipering method of determining prism power. This method, as we stated, is best applied to Plano prisms but may be applied to any prismatic lenses by first calculating the thickness difference caused by the correction—a tedious procedure. A very simple method of determining the prism power of any lens is by means of a calibrated scale.

This method is based on the universally accepted definition of a prism diopter by C. F. Prentice in 1886. Agreeable to this definition a one diopter prism produces a

deviation of one centimeter at a distance of one meter. Therefore, at a distance of one meter a five diopter prism would produce a deviation of five centimeters and so on.

To use this principle for measuring prism power, it is necessary to have a scale hung on a wall at a known distance from the prism to be measured. We suggest using an 18 inch ruler, which is easily obtained, as a means of obtaining a fixed distance. One end of the ruler is placed below the zero mark on the chart, see cut, and the prism is held on the opposite end of the ruler with the apex of the prism down. The line on the chart corresponding to the power of the prism will fall on the zero line.

To figure the separation of the lines on the chart is a simple problem in ratio. If an 18 inch ruler is to be used as the distance from prism to scale, the separation of the lines must be 4.572 millimeters. 18 inches equal 457.2 millimeters, therefore, 1000 is to 10 as 457.2 is to x . x equals 4.572 millimeters. If a 12 inch ruler is used, the distance between the lines must be 3.048 millimeters. At two feet the lines on the scale would be 6.096 millimeters apart.



"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

AMERICAN JOURNAL OF OPHTHALMOLOGY

SERIES 3 • VOLUME 36 • NUMBER 6, PART I • JUNE, 1953

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ABSTRACTS

Anatomy, embryology, and comparative ophthalmology; Vegetative physiology, biochemistry, pharmacology, toxicology; Physiologic optics, refraction, color vision; Diagnosis and therapy; Ocular motility; Conjunctiva, cornea, sclera; Uvea, sympathetic disease, aqueous; Glaucoma and ocular tension; Crystalline lens; Retina and vitreous; Optic nerve and chiasm; Neuro-Ophthalmology; Eyeball, orbit, sinuses; Eyelids, lacrimal apparatus; Tumors; Systemic disease and parasites	872
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SURGICAL CORRECTION OF BLEPHAROPTOSIS*

RAYNOLD N. BERKE, M.D.

Hackensack, New Jersey

Despite the fact that almost 90 different operations have been recommended for the correction of ptosis, the surgical treatment of this deformity is still, in some respects, one of the unsolved problems in ophthalmology. This is so partly because of the inherent limitations of all ptosis operations but mostly because of the diverse and complicated nature of ptosis. For these reasons the surgeon cannot expect to produce an entirely satisfactory cosmetic and functional result in all cases.

CRITERIA FOR A PERFECT PTOSIS OPERATION

Some of the criteria for a perfect ptosis operation are: (1) The upper lids should cover the two corneas equally (fig. 1); (2) the curve of the upper lids should match in contour and shape, with no tendency to form a notch or to invert the lashes; (3) both upper lid folds should correspond in position and shape; (4) the width of the palpebral fissures should be equal, and the upper lids should move synchronously with the two corneas, in all directions of gaze; (5) the vertical distance between the eyebrow and the upper lid margin should be the same on the two sides; (6) normal winking should be preserved; (7) the lids should close normally in sleep; (8) diplopia and hyperopia should be absent.

Such a result is a physical impossibility in all cases of ptosis, not because of a dearth of ptosis operations but, as will be pointed out,

because of the complicated nature of some types of congenital ptosis.

LIMITATIONS OF PTOSIS OPERATIONS

The many surgical procedures designed to correct ptosis may be placed in one of three groups:

I. FRONTALIS MUSCLE TYPE OF PTOSIS OPERATION

These procedures suspend the lid from the brow, thus utilizing the lifting power of the frontalis muscle to support the upper lid. The chief disadvantages of this type of operation are the lagophthalmos present in looking down and the corrugation of the forehead with elevation of the brow in looking up. Therefore, these operations seldom give satisfactory results, especially in monocular ptosis. They represent, however, the operation of choice in bilateral complete ptosis associated with paralysis of ocular elevation with little or no levator action.

In one of my cases all the extraocular muscles appeared to be bands of connective tissue at the time of operation; in two other cases the inferior rectus muscles were fibrous. Because of the poor levator action present in these two cases, suspending the upper lids from the brow was the operation of choice.

II. SUPERIOR RECTUS MUSCLE TYPE OF PTOSIS OPERATION

The success of these procedures depends on the formation of adhesions between the tissues of the upper lid and the superior rectus muscle. Their chief disadvantages are:

* Presented at the 38th annual clinical congress of the American College of Surgeons, New York, September, 1952.



Fig. 1 (Berke). Illustrating the criteria of a perfect result from ptosis surgery. Note that the position and curve of the upper lids and the upper-lid folds are equal on the two sides, the width of the fissures and the distance from the upper-lid margins to the brows are the same, and that the lids move synchronously with the globe in looking up and in looking down. Such a result is impossible in all cases of ptosis.

a tendency to notch formation of the upper lid, an induced weakness of the superior rectus muscle, and an inclination to lagophthalmos in sleep.

The first two of these disadvantages can be greatly minimized if the superior rectus muscle is shortened and a broad adhesion formed between the lid and the superior rectus muscle at the time of the ptosis operation, according to the technique already described.¹ Practically all of these patients with laophthalmos develop a modified Bell's phenomenon during sleep and a resistance of the corneal epithelium to drying so that corneal ulceration does not develop.

The main advantage of the superior rectus operation is the synchronous movement of the lid with the cornea in all directions of gaze.

III. SHORTENING OF THE LEVATOR PALPEBRAE MUSCLE FOR PTOSIS

The success of these procedures depends on the presence of adequate levator tissue from which to support the upper lid.

Their chief disadvantage is the tendency to undercorrection. However, because of the excellent cosmetic and functional results usually obtained, resection of the levator is generally accepted as the operation of choice in all cases of ptosis when adequate levator tissue is present (except, of course, when the ptosis is associated with the jaw-winking phenomenon of Marcus Gunn).

TYPES OF CONGENITAL PTOSIS

The nature of the ptosis in a given case is a most important consideration in determining not only the type of operation to be done but also the success of the operation selected. For example, in a recent survey² of the results on 91 consecutive operations of resection of the levator, it was shown that the percentage of good and excellent results varied from as little as 30 percent to as much as 78 percent, depending on the nature of the ptosis present.

Because congenital ptosis is more common than the acquired variety, and because the etiology of the latter is so varied and the treatment so individualized, this discussion will be devoted entirely to the congenital type.

In order to give an over-all picture of the variable nature of congenital ptosis, 200 consecutive cases were critically examined and the data tabulated³ (fig. 2). This showed that congenital ptosis may be divided into four distinct groups. (Spaeth⁴ divides congenital ptosis into nine groups.)

GROUP 1

Group 1 was made up of patients with normal functioning superior rectus muscles, about one half of whom had good levator action. When this entire group was subjected to an operation for resection of the levator, irrespective of the degree of levator action present, it was demonstrated that 66 percent

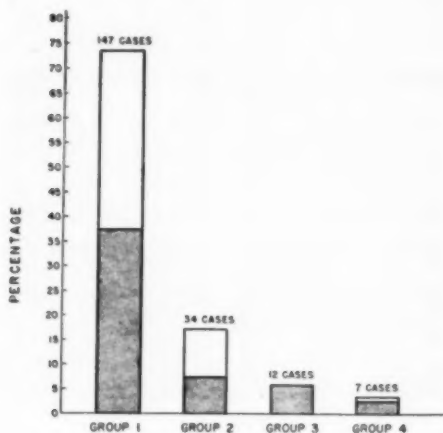


Fig. 2 (Berke). Classification of 200 cases of congenital ptosis. Group I indicates patients with normal superior rectus muscles; Group 2, patients with weak superior rectus muscles; Group 3, patients with ptosis and the jaw-winking phenomenon of Marcus Gunn; Group 4, patients with ptosis and blepharophimosis. The clear rectangles indicate the percentage of each group having poor levator function, and the black rectangles the percentage with relatively good (but not normal) levator muscle action.

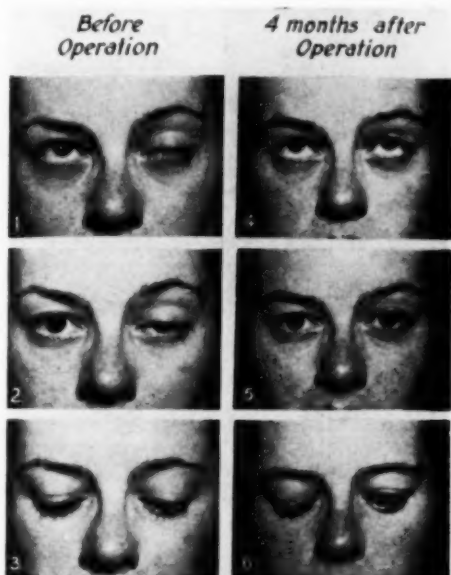


Fig. 3 (Berke). Illustrating an excellent post-operative result in a case of congenital ptosis of four mm. in the primary position with a normal superior rectus muscle and relatively good levator muscle function (group 1). Compare 1 with 4, 2 with 5, and 3 with 6 and note that the upper lids and upper-lid folds match in position and contour in looking up and in the primary position. The lagophthalmos on the left, present in looking down, has been exaggerated by shortening the levator muscle, but cannot be avoided because of the non-elasticity of the muscle.

derived a good or excellent result from the operation.³

When, however, the levator action was good, the percentage of good or excellent results increased to 78 percent (fig. 3); when it was poor, this percentage dropped to only 57 percent. Thus, it is obvious that the nature of the ptosis in this group determined the percentage of satisfactory results obtained from the operation.

GROUP 2

Group 2 consisted of patients with definite clinical weakness of the homolateral superior rectus muscle. In each case, resection of the



Fig. 4 (Berke). Illustrating a good result in a patient with congenital ptosis associated with a weak superior rectus muscle and poor levator action (group 2). Compare 1 with 4, 2 with 5, and 3 with 6. Note that there is little movement of the right eye or of the right upper lid in looking up or down before and after operation. The postoperative hypotropia in looking up and the lagophthalmos in looking down must be attributed to the nature of the ptosis.

levator was done to correct the ptosis with a good or excellent result in only 47 percent of the cases, compared to 66 percent for Group 1.² These comparative figures demonstrate that the percentage of adequate results following resection of the levator depends a great deal on the nature of the ptosis present—specifically, in this instance, on the function of the superior rectus muscle.

When the patients in Group 2 were divided into two subgroups—that is, cases with good levator action and cases with poor levator action—and the effects of resection of the levator for each subgroup were compared, it was discovered that 50 percent of the former and only 30 percent of the

latter got satisfactory results (fig. 4). Thus it is clear that the good or excellent effects of this operation in congenital ptosis are determined not only by the degree of levator action present but also by the function of the homolateral superior rectus muscle.

From a practical point of view, it is unfortunate that all patients with congenital ptosis do not fall into Group 1 with good levator action, where satisfactory results may be expected in 78 percent of the cases.

Since a large percentage of these operations were done by the resident staff, few of whom had the opportunity of performing more than two or three of these opera-



Fig. 5 (Berke). Illustrating a poor result in a patient with ptosis and the jaw-winking phenomenon of Marcus Gunn (group 3) following a Friedenwald-Guyton frontalis ptosis operation. Compare 1 with 4, 2 with 5, 3 with 6. Note that the patient has residual ptosis in looking up and in the primary position with slight lagophthalmos in looking down postoperatively. With a conscious effort he can elevate the right upper lid almost to equal the position of the left, but he habitually carried both brows in a normal position. As a result, he has ptosis in all directions of gaze except in eyes down. This result is typical of most cases of monocular ptosis in which the lid is suspended from the brow.

Before Operation*After Operation*

Fig. 6 (Berke). Illustrating a good result from a modified Motais-Parinaud operation (in which the superior rectus muscle was shortened, a portion of the levator excised and the lid suspended from the superior rectus muscle) in a case of ptosis associated with the jaw-winking phenomenon of Marcus Gunn and moderate weakness of the superior rectus muscle (Group 3). Note the postoperative improvement of the ptosis with the jaw slightly to the left (compare 1 with 4), the absence of ptosis before and after operation with the jaw depressed (compare 2 with 5) and the marked postoperative improvement in the ptosis with the jaw moved to the right (compare 3 with 6). (See figure 7 for position of the lids in looking up and in looking down before and after operation.)

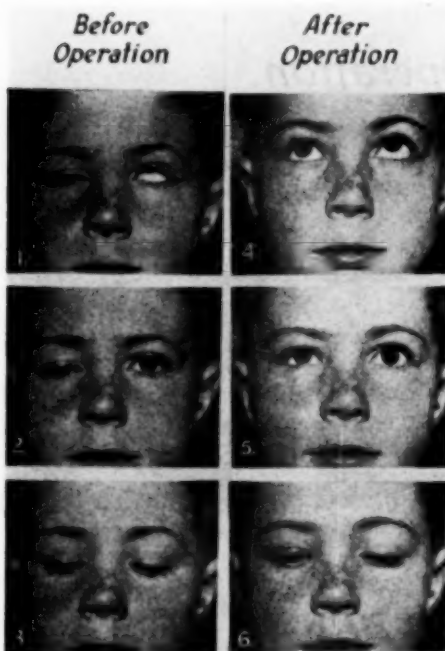


Fig. 7 (Berke). Illustrating the position of the upper lids in different directions of gaze before and after operation with the jaw closed normally (same case as in figure 6). Views 1, 2, and 3 show the amount of ptosis in looking up, in the primary position, and in looking down before operation but do not show the weakness of the right superior rectus muscle. Compare 1 with 4 and note the residual right hypotropia after operation even though the superior rectus muscle has been shortened six to eight mm. (no diplopia because O.D. is amblyopic). Compare 2 and 5 and note the marked improvement of the ptosis. The slight lagophthalmos in looking down (view 6) is to be expected because the upper lid, O.D., is anchored to the globe. (Photographs taken six weeks after operation.)

tions during the entire residency, even better results should be obtained with experience and improved technique.

The most unfortunate were those patients in Group 2 who had weakness of the homolateral superior rectus muscle combined with poor levator action. In these, not only was the percentage of good results from resection of the levator comparatively low (30 percent) but the percentage of horizontal deviations was extremely high. For example,

in Group 1 only 7.3 percent of the patients had esotropia or exotropia, while in Group 2, 66 percent were thus affected.²

GROUP 3

Group 3 consisted of ptosis associated with the jaw-winking phenomenon of Marcus Gunn. In all cases, good levator action was present, especially when the jaw was depressed or moved to the opposite side. Some weakness of the homolateral superior rectus muscle was noted in 73 percent of the cases, usually associated with overaction of the contralateral inferior oblique muscle.

These patients presented a special problem; not only was it necessary to correct the ptosis and the bizarre behavior of the upper lid but the hypotropia as well. In two of our cases in which the jaw-winking was slight and the superior rectus muscle completely paralyzed, a liberal resection of the levator muscle was done with failure in both cases.

In two other cases, Spaeth's⁸ suggestion was followed and a piece of the levator muscle was excised and the lid suspended from the brow; the results were unsatisfactory in both cases (fig. 5).

In other cases a piece of the levator was excised, the homolateral superior rectus shortened, and the upper lid sutured to the tendon of the superior rectus muscle according to the technique described in 1949.¹ In two of these cases, the result was excellent (figs. 6 and 7), in four it was good, and in one the operation was a failure.

In the two cases in which the upper lid was suspended from the brow, the patients were able to elevate the ptotic lid by contracting the frontalis muscle voluntarily when requested to do so; however, they habitually carried both brows in a relaxed and normal position so that normally the operated lid remained in a ptotic position.

Even in the cases in which the result was considered to be good or excellent, it was not perfect, because in each case some residual hypotropia could be brought out in the upper fields (fig. 7) (even though the

superior rectus muscle had been shortened), normal winking was disturbed, and the lids could not be closed normally in sleep.

Thus, although the postoperative cosmetic and functional result was considered gratifying in some of these cases (considering the surgical problem present), one is forced to the conclusion that the nature of ptosis in patients with the jaw-winking phenomenon is such a perfect result is surgically impossible in the light of our present knowledge.

GROUP 4

Group 4 was made up of seven cases of ptosis associated with blepharophimosis characterized by very short fissures horizon-

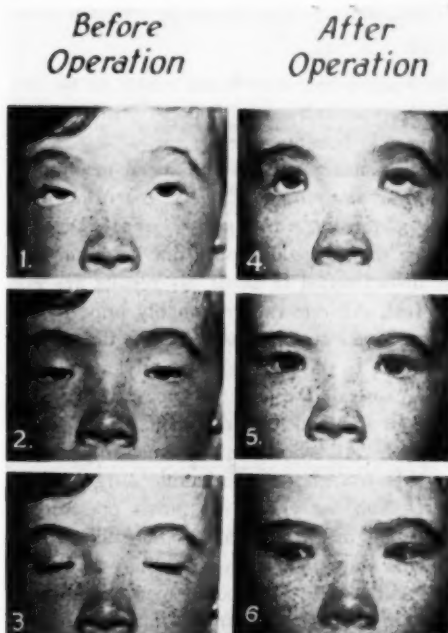


Fig. 8 (Berke). Illustrating the postoperative result of bilateral resection of the levator in a case of ptosis associated with mild blepharophimosis (group 4). In this seven-year-old girl, the fissures measured only 22 mm. horizontally but the distance between the inner canthi was 42 mm. After operation both pupils are uncovered in the primary position and the eyebrows are no longer elevated. The normal-appearing upper lid folds augment the cosmetic result.

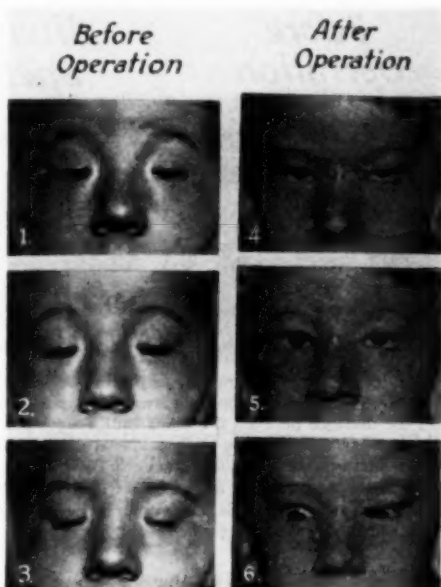


Fig. 9 (Berke). Illustrating the postoperative result in a case of moderately severe blepharophimosis (group 4) in which each fissure measured 20 mm. horizontally and the distance between the inner canthi 35 mm. preoperatively. A modified Von Ammon operation, in which the subcutaneous tissues were overlapped, resulted in a scar over the bridge of the nose and a decrease of the intercanthal distance from 35 to 28 mm. A bilateral Friedenwald-Guyton frontalis operation later corrected the ptosis fairly well with some residual postoperative ptosis in looking up and lagophthalmos in looking down. Later the left upper lid became infected, the left ptosis increased and the stainless steel wire had to be replaced.

tally and an abnormally great distance between the inner canthi. In three cases the shortened fissures were displaced so far laterally that both pupils were partly covered by the inner canthi in the primary position.

Some of these cases present a most difficult surgical problem because usually it is necessary to lengthen the fissures as well as correct the ptosis. In mild cases it was not necessary to lengthen the fissures because, although shorter than normal, the fissures were properly placed in front of the two pupils. In severe cases of blepharophimosis we have found external blepharoplasty sat-



Fig. 10 (Berke). Illustrating the postoperative result in a case of ptosis associated with marked blepharophimosis (group 4). When the patient was aged four years, each fissure measured only 13 mm. horizontally and the distance between the inner canthi was 45 mm. (view 1). After shortening the inner canthal ligaments and lengthening the fissures laterally, each upper lid was suspended from the corresponding superior rectus muscle with the result shown in View 2. Because the inner canthus partly covered each cornea in the primary position, the fissures were lengthened nasally, after which both lids were suspended from the frontalis muscle via stainless steel wires. The poor final result, shown in View 3, must be attributed to the complicated nature of the ptosis.

isfactory for increasing the length of the fissures laterally, but to date we have found no entirely satisfactory method for lengthening the fissures nasally.

In one case of ptosis with blepharophimosis, resection of the levator was a complete failure; in four other cases, this operation corrected the ptosis satisfactorily (fig. 8); in two other cases the lids were suspended from the brow with a fair result in each case (fig. 9). In one case the final cosmetic result was entirely unsatisfactory, even when the ptosis was partly corrected, because of the irregular curvature of the palpebral fissures (fig. 10).

Ptosis associated with blepharophimosis, therefore, represents one of the unsolved problems in ophthalmology.

DISCUSSION

Since this article has stressed the difficulties and frustrations to be encountered in the surgical treatment of congenital ptosis, the impression may be given that the purpose of this paper is to discourage surgery in the more complicated cases. On the contrary, I believe these problem cases should be given the benefit of surgery because, even though

the final result may leave much to be desired, practically all of these patients can be greatly benefited.

My primary purpose has been to emphasize that *the nature of the ptosis in a given case determines the nature of the result*. Thus, the surgeon should not be apologetic or disheartened if all of his results are not perfect. All one can reasonably hope to accomplish in any case is to utilize the tissues available to the patient's best advantage.

Because of the unsatisfactory results, one may be inclined to agree with Beard⁶ when he said, "All who have had much experience in this branch of ophthalmic surgery will agree that the results of ptosis operations, taken all in all, are far from brilliant."

This statement is as true today as it was 38 years ago. The point to remember is that, in the great majority of patients with congenital ptosis, the *results can be "brilliant."* When these results are "far from brilliant," the cause for failure is to be attributed more to the nature of the ptosis itself than to a fault of the surgeon.

SUMMARY AND CONCLUSIONS

It is impossible to produce a perfect cos-

metic and functional result in every case of congenital ptosis because of the inherent limitations of all ptosis operations and because of the complicated nature of some cases.

All cases of congenital ptosis may be classified into one of four groups: Group 1, ptosis with normal superior rectus muscle function; Group 2, ptosis with weakness of the homolateral superior rectus muscle; Group 3, ptosis with the jaw-winking phenomenon of Marcus Gunn; Group 4, ptosis associated with blepharophimosis.

In Group 1, resection of the levator produces a good or excellent result in from 57 to 78 percent of the cases, depending on the amount of levator action present.

In Group 2, these figures drop to 30 per-

cent and 50 percent, respectively.

In Group 3, resection of the levator is contraindicated. Here the jaw-winking must be destroyed by excising a piece of the levator and the ptosis corrected by other means.

Group 4 presents a surgical challenge for the correction of the blepharophimosis as well as the ptosis.

In general, resection of the levator is the operation of choice in all types of congenital ptosis, especially when relatively good levator action is present.

430 Union Street.

I am deeply indebted to my colleagues at the Eye Institute, Presbyterian Hospital, New York, for the opportunity to study and report the cases illustrated in this article.

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OPHTHALMIC MINIATURE

On Itching and Inflammation of the Eyelids

Sometimes the blood in the brain becomes melancholic and thence runs into the eyes, inducing extreme dryness of the lids. This in turn causes severe itching and burning of the eyes and eyelids, chiefly because the afflicted one was not purged at once and did not abstain from harmful food. Such a patient should, if young, be bled from the medial frontal vein and treated with the following collyrium: Take forty tender buds of the sloe and pound them thoroughly. Mix them with two measures of good wine and boil them in a new pot to one-half, when the mixture should be removed from the fire and strained. This decoction dropped into the eye will restore it to health.

Benevenutus Grassus of Jerusalem,
De Oculis Eorumque Egritudinibus et Curis,
Translated by Casey A. Wood, 1929.

UPTAKE OF RADIOACTIVE PHOSPHORUS BY NORMAL AND NEOPLASTIC OCULAR TISSUES*

EDWIN B. DUNPHY, M.D., AND BERTRAM SELVERSTONE,† M.D.
Boston, Massachusetts

With a view to its possible application to the diagnosis of various intraocular masses and of retinal separations, studies of the uptake of radioactive phosphate ion by ocular tumors and by the normal ocular tissues were undertaken in January, 1949. An initial report¹ was made in November, 1950, at which time it was concluded that P^{32} , administered parenterally, assumed a higher concentration in the vascular tissues of the eye than in the less vascular tissues. The lens, cornea, and the intraocular fluids also showed low concentrations of the isotope.

Silverstone and Solomon² had previously found a strikingly higher uptake of labeled phosphate ion by brain tumors than by normal brain. Using the probing Geiger-Müller counter of Robinson,³ these differences have been utilized for the localization and demarcation of intracerebral tumors.^{4, 5}

It seemed worth while, therefore, to investigate the possibility that P^{32} might localize in certain intraocular tumors sufficiently to permit their verification by means of some modification of the neurosurgical probing counter.

METHOD

Each patient (except B. B.) received a single intravenous dose of from 0.15 to 1.4 millicuries of buffered radioactive phosphate ion (P^{32}) from 16 to 24 hours before enucleation. One patient (B. B.), who had no ocular pathologic condition, received 3.9 mc. of P^{32} for localization of a malignant brain tumor. She died on the second postoperative

day, 83 hours after the injection, and an eye was obtained at postmortem examination. The other enucleations were performed surgically for tumor, traumatic glaucoma, or posttraumatic degeneration.

Samples of each of the ocular and extraocular tissues shown in Table 1 were obtained and labeled by an ophthalmic surgeon immediately after operation. The remainder of the globe was fixed and examined in the Pathology Laboratory of the Massachusetts Eye and Ear Infirmary.

Weighted aliquots, usually from 50 to 75 mg., were taken from each tissue sample, dried, and assayed by means of an end-window Geiger-Müller counter. Because of the high energy of the beta emission of P^{32} , no correction has been made for self-absorption.

Since the cornea is a homogeneous, avascular tissue of low P^{32} uptake, its activity has been used as a base line in order to eliminate variations in radioactivity caused by differences in dose or in body weight.

$$\text{The ratio} = \frac{\text{counts/min./mg. in tissue}}{\text{counts/min./mg. in cornea}}$$

will be called the "activity ratio" of the tissue. In one case (A. A.) the cornea was markedly scarred. In this instance, the ratio has, therefore, been calculated with respect to sclera, which was normal. Observations in other cases showed that the activity of the normal cornea was from 0.71 to 1.9 times that of sclera. In A. A. the scarred cornea was only 0.36 times as active as the sclera.

RESULTS

It is clear from Table 1 that the uptake of P^{32} under the conditions of this study has been far less in cornea, sclera, aqueous, vit-

*From the Ophthalmic Service, Massachusetts Eye and Ear Infirmary, the Neurosurgical Service of the Massachusetts General Hospital, and the Departments of Ophthalmology and Surgery, Harvard Medical School.

†Now Professor of Neurosurgery, Tufts College Medical School.

TABLE 1
ACTIVITY RATIOS OF NORMAL AND PATHOLOGIC OCULAR TISSUES AFTER
INTRAVENOUS INJECTION OF P^{32}
(Normal cornea = 1.0 except as noted in case A. A.)

Date	1/18/49	2/18/49	2/24/49	4/11/49	9/10/49	1/19/51	3/9/51	6/6/51
Patient	A. A.*	B. B.†	R. E.‡	P. W.	G. H.	M. L.	C. M.	H. T.
Age (yrs.)	57	64	29	59	40	2	1	1
Δt hrs. (approx.)	16	83	20	24	23	20	17	18
Melanoma				5.6	3.2			
Retinoblastoma						8.3	7.2	50.7
Cornea	0.36 (scarred)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aqueous	0.13	0.51	0.19	0.59				
Vitreous	0.10	0.20	0.18	0.19				
Lens		0.79		0.48	0.52			
Retina	2.6	2.8	5.3	1.7	1.2	4.5	4.3	
Choroid	5.9	3.0	4.7	2.3	6.7	5.2	2.4	
Optic nerve	2.3	3.7	1.4	1.3				
Sclera	1.0	1.4	0.70	1.0	1.3		0.54	0.68
E.O.M.	1.0	3.1		1.5	0.89			
Retrobulb. fat		0.68		1.3				
Iris and ciliary body	2.8	2.4	4.8	2.5	1.3	4.3	1.7	3.3

* A. A.—Posttraumatic degeneration with scarred cornea. Sclera = 1.0.

† B. B.—Normal eye removed at autopsy.

‡ R. E.—Absolute glaucoma with hemorrhage, secondary to trauma (see text).

reous, and lens than in the more vascular tissues of the eye. In each neoplastic eye, with the exception of G. H., activity of the tumor was higher than that of any of the other ocular or extraocular tissues studied, including the more vascular tissues. In two cases of retinoblastoma (M. L. and C. M.), in which supposedly normal retina was assayed, activity ratios for this tissue were quite high. Infiltration of adjacent ratios by these extensive neoplasms may have been responsible for this finding. Counts from the choroid were unusually high in one eye with melanoma (G. H.) and one with retinoblastoma (M. L.). A similar explanation is suggested.

In one case where no tumor was present (R. E.), there was a surprisingly high activity ratio in retina, choroid, and iris. Pathologic examination of this glaucomatous eye showed extensive sanguinous separation of the choroid, with recurrent bleeding into the retina, diffuse congestion of choroidal vessels, and vascularization of the iris.

DISCUSSION

These results suggest that there is a dif-

ferential uptake of P^{32} in certain ocular tumors as compared with the normal tissues of the eye. The possible application of this observation to in vivo studies both before and during operation is obvious.

It should be pointed out, however, that the retina and choroid may show abnormally high counts in neoplastic eyes. The presence of a high counting rate, therefore, over one portion of an eye may indicate the presence of a neoplasm but not necessarily its precise site. A melanoma several times the choroid in thickness might be detectable in vivo through the sclera, in spite of an activity, weight for weight, less than that of normal choroid.

Until much more extensive data are available, however, we warn against reliance upon such studies as these, if they suggest a course of action which differs from a decision made independently on clinical grounds.

Thomas, Krohmer, and Storaasli⁶ have used P^{32} in an attempt to detect intraocular tumors of the anterior half of the globe by means of an external counter. One of us (E. B. D.) is investigating a modification of the Robinson-Silverstone neurosurgical

counter* for the diagnosis of tumors in the posterior half of the globe.

Another possibility is suggested by the report of Selverstone, Sweet, and Ireton⁷ concerning the concentration of K^{42} in cerebral tumors. It is possible that direct external counting of the gamma rays of an isotope such as K^{42} may provide useful information concerning the presence of an intraocular tumor.

SUMMARY

Data are reported in eight cases concern-

* Obtainable from Robert A. Waters, Inc., Waltham, Massachusetts.

Pathologic examinations were made by Dr. Parker Heath.

ing the relative uptake of radioactive phosphorus by various ocular and extraocular tissues. In five of these cases an intraocular tumor was present. The uptake of P^{32} in three retinoblastomas was significantly higher than that of the other ocular tissues and suggests the possibility that diagnosis of this tumor by means of a miniature in vivo counter may be feasible. In one of two melanomas the activity ratio was actually less than that of the normal choroid, although higher than other ocular tissues. This imposes a relative but not an absolute impediment to the possible application of in vivo counting to such cases.

243 Charles Street (14).

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OPHTHALMIC MINIATURE

The Glandulae Lachrymales are often infected, and do according to the variety of their disorders produce several sorts of Tumours about the eye; the most usual of which is a Lippitudo, an affection of the ends of the Lachrymal Vessels, which being derived from them do terminate near the cilia, so also the Hordeoli, etc., nay it is not rare to see the whole ball of the Eye thrust out by the Tumour of these Glandules. Ophthalmia it self is often a consequent of the Disease; so is also the Fistula Lachrymalis which often oweth its origin to this cause.

Richard Wiseman,
A Treatise of the King's-Evill, 1696.

THE EFFECT OF HYALURONIDASE ON THE THERAPEUTIC EFFICACY OF BAL APPLIED TO RABBIT CORNEA*

CHARLES HARRIS, CAPT. (MC) U.S.A., AND BERNARD S. COHEN, LIEUT. (MC) U.S.A.
Army Chemical Center, Maryland

There has been conflicting evidence in the literature concerning the effect of hyaluronidase on the penetration of the cornea by liquids. Meyer and Chaffee¹ stated that the cornea contains hyaluronosulfate and described its hydrolysis by hyaluronidases prepared from testes and pneumococci. Wislocki and others² failed to demonstrate alterations in metachromasia in corneas treated with hyaluronidase, and Woodin,³ unable to demonstrate any effect by hyaluronidase on the spread of liquids through the cornea, suggested that impurity in the hyaluronidase extract may have been responsible for the results reported by Meyer and Chaffee.

This suggestion may be valid since a mucinase has recently been separated from testicular extracts of hyaluronidase,⁴ and since Woodin has recently stated that corneal mucopolysaccharide is not a substrate for hyaluronidase.⁵

The possibility of mild lewisite vapor burns of the eye, and more severe splash burns by small droplets, is a constant hazard to plant and laboratory workers dealing with this substance. For BAL to be effective in these cases it must be applied immediately and, if the application of this substance is delayed for even three or four minutes, irreparable damage may occur. Increasing the speed of absorption of BAL from the conjunctival sac, and enhancing its rapid, even distribution through the cornea is desirable, despite the marked efficiency with which BAL is known to work.

METHOD

This experiment tests the effect of hyaluronidase on the therapeutic efficacy of BAL, when used to treat lewisite burns. Black rabbits with pigmented eyes were used for the

test. The eyes were checked before burning and those rabbits with corneal opacity or iridal inflammatory changes were discarded.

Three experiments were done in which eye burns of varying severity were treated with five-percent BAL dissolved in ethylene glycol, with and without admixed hyaluronidase. The burned eyes of one group of rabbits were treated with hyaluronidase alone.

Lewisite-vapor exposures were carried out at room temperature (22 to 26°C.) by placing the evulsed eye of ether anesthetized rabbits over a properly fitting vapor cup containing lewisite in which a small fan made of filter paper was continually rotated by hand (fig. 1).

A fresh vapor cup filled with 0.4 cc. lewisite was used to expose each 20 eyes, an additional 0.2 cc. lewisite being added to the cup after it had been used to expose 10 eyes. One drop of lewisite liquid was applied to the fan each time lewisite was added to the cup. Under the conditions of the experiment, temperature variation was too small to warrant immersion of the vapor cup in a constant temperature bath.

The lewisite used was at least 99-percent pure by arsenic and 99-percent pure by chloride analyses. American reference standard BAL in ethylene glycol was employed.

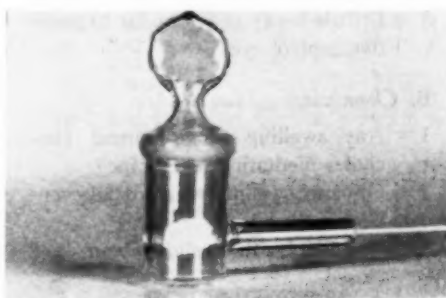


Fig. 1 (Harris and Cohen). The vapor cup.

* From the Chemical Corps Medical Laboratories.

The extent of each burn was evaluated by the scoring system detailed below:

SCALE OF EVALUATION⁶

I. CORNEA

A. *Opacity*: Degree of density (if one area is more dense than another, the reading is taken as that of the most dense area):

- 0 = No visible lesion
- 1 = Scattered or diffuse area. Details of iris clearly visible
- 2 = Easily discernible translucent areas. Details of iris slightly obscured
- 3 = Opalescent areas. No details of iris visible but size of pupil barely discernible
- 4 = Opaque. Iris invisible

B. *Area of cornea involved*:

- 1 = $\frac{1}{4}$ (or less) other than 0
- 2 = Greater than $\frac{1}{4}$ and less than $\frac{1}{2}$
- 3 = Greater than $\frac{1}{2}$ and less than $\frac{3}{4}$
- 4 = Greater than $\frac{3}{4}$ up to and including whole area

Score = $(A \times B) \times 5$. Maximum = 80

II. CONJUNCTIVAS

A. *Redness* (refers to palpebral conjunctivas only):

- 1 = Vessels definitely injected above normal
- 2 = More diffuse, deeper crimson red—individual vessels not easily visible
- 3 = Diffuse beefy red—similar to positive control eyes

B. *Chemosis*:

- 1 = Any swelling above normal (includes nictitating membrane)
- 2 = Obvious swelling with partial eversion of the lids
- 3 = Swelling with eyelids about half closed
- 4 = Swelling with the eyelids from one-half closed to fully closed

C. *Discharge*:

- 1 = Any amount different from normal (does not include the tiny amount observed in the inner canthus of normal animals)
- 2 = Discharge with moistening of the lids and hair just adjacent to the lids
- 3 = Discharge with moistening of the hair and considerable area around the eye

Score A + B + C \times 2. Maximum = 20

The total score therefore is 100. Another 10 points can be distributed for iris lesions, but 24 hours after exposure the opacities of the cornea may prevent one's observation of the iris. For this reason, we omitted iris evaluation.

The eyes were examined once 24 hours after the vapor exposure. After exposure to liquid lewisite, the eyes were examined 10 times over a three-week period; every 24 hours for the first five days, then approximately every other day for the following two weeks.

Eyes exposed to lewisite vapor, then treated with BAL, with resultant scores between 0 and 60, need not be examined more than once after 24 hours, because differences between two groups of eyes, one treated with BAL alone and the other with BAL plus hyaluronidase, are statistically determinable at this time.

PROCEDURE

IN EXPERIMENT I, the eyes of rabbits in each of four groups were exposed to vapor from concentrated lewisite for 30 seconds as specified in Military Specifications for BAL.⁶ In each group the eyes of five rabbits were treated as scheduled below, and one rabbit was kept as an untreated control.

Group I. One minute after burning, eyes were treated with 0.1 cc. of five-percent BAL dissolved in ethylene glycol.

Group II. One minute after burning, eyes were treated with 0.1 cc. of a five-percent solution of BAL in ethylene glycol in which

150 turbidity reducing units of hyaluronidase were dissolved.

Group III. One minute after burning, eyes were treated with 0.1 cc. of an ointment of five-percent BAL in a glycol base.

Group IV. One minute after burning, eyes were treated with 0.1 cc. of an ointment of five-percent BAL in a glycol base to which 150 turbidity reducing units of hyaluronidase were added.

EXPERIMENT II was devised to test the effect of hyaluronidase-BAL mixtures on burns more severe than those obtained in Experiment I. Increased burn scores (from 30 to 50) enable one to determine the significance of smaller score decrements due to the test substance, with smaller numbers of animals, than can be done with scores in the range 0 to 20 (see discussion).

There are three ways of increasing vapor burn scores in BAL-tested eyes: (1) To increase the amount of time that the eye is exposed to vapor; (2) to expose the eye for the routine 30 seconds but delay treatment from the usual one minute after exposure ceases to longer periods of time; (3) (a method we did not employ) to increase the temperature of the lewisite to increase the vapor concentration.

In the first portion of this experiment, the eyes of 16 rabbits were burned with lewisite as already detailed. The burned eyes of two rabbits were not treated. One eye of each of the remaining rabbits was treated four minutes after burning with 0.1 cc. of five-percent BAL dissolved in ethylene glycol, while the second eye was treated four minutes after burning with the same mixture, to which 150 turbidity reducing units of hyaluronidase were added.

In the second part of the experiment the eyes were exposed to lewisite vapor for one minute (twice the prescribed exposure), one eye treated with BAL and the other with BAL plus hyaluronidase 30 seconds after exposure. Therefore, although the exposure time was doubled, the time of treatment was one and one-half minutes after exposure was

started, which is the same time after the start of exposure that treatment is advised in the Military Specifications BAL.⁶

IN EXPERIMENT III, the eyes of 12 rabbits were burned with one drop of liquid lewisite from a 24-gauge hypodermic needle. Four control eyes were not treated. Ten of the remaining 20 eyes were treated with BAL alone and the other 10 were treated with the BAL liquid mixture with added hyaluronidase one minute after exposure. The scoring specifications detailed previously were used and analysis of variance was performed to determine whether the hyaluronidase significantly altered the therapeutic efficiency of BAL.

RESULTS

In no instance did hyaluronidase alter the nature of the therapeutic response to BAL of eyes burned with lewisite (table 1). The hyaluronidase did not significantly change the course of lewisite burns which were not treated with BAL.

In Experiment I, an excellent therapeutic effect was obtained in all animals. In Experiment II, all 24-hour burns were more severe

TABLE 1
AVERAGE EYE SCORES FOR EXPERIMENTS I, II, III

Experiment No.	Treatment	Number of Eyes Treated	Average Score
1	BAL liquid	10	14.5 ± 4.9
	BAL liquid with added hyaluronidase	10	18.3 ± 4.8
	BAL ointment	10	13.0 ± 6.4
2A	BAL liquid with added hyaluronidase	8	4.1 ± 1.9
	BAL liquid	14	39.0 ± 6.8
	BAL liquid with added hyaluronidase	14	40.6 ± 5.6
2B	BAL liquid	8	20.1 ± 9.4
	BAL liquid with added hyaluronidase	8	26.3 ± 11.4
	BAL liquid	10	110*
3	BAL liquid with added hyaluronidase	10	110
	BAL liquid		
	BAL liquid with added hyaluronidase		

* Since all eyes in this group received top score 24 hours after burning, there is no determinable scoring variation.

than those of Experiment I, and all eye changes except one were considered reversible.

In Experiment III, one eye recovered and all others were irreparably damaged; corneal perforation occurred in more than 50 percent of the eyes after the third week of observation.

DISCUSSION

BAL penetrates the cornea rapidly, so that only a potent, rapid acting agent could increase its efficiency. This experiment shows that hyaluronidase fails to increase the efficiency of BAL, but does not determine the action of hyaluronidase on the cornea.

It is possible that hyaluronidase may be effective in aiding corneal penetration by an agent which would penetrate only very slowly. Because of the normal high efficiency of BAL, and the large variation in scores of lewisite-burned eyes treated with BAL, the experiments herein described will detect only large enhancing effects on BAL that hyaluronidase might exert.

BAL will theoretically prevent the inhibition of enzyme systems by arsenic. The damage from this action, however, will not be immediately apparent. In eyes exposed to splash burns the cornea turns milk white the moment the liquid makes contact with it.

This immediate effect cannot be attributed to the arsenical action, but is probably due to the combination of the hygroscopic effect of the lewisite, and the acid effect and protein denaturation resulting from the hydrolysis of lewisite when it comes in contact with the lacrimal secretions. This component of the burn should not be affected by the BAL.

The arsenic effects should be completely reversed by BAL in mild vapor exposures. The large variation in response, between animals and between similarly treated eyes in the same animal, as measured by the scoring specifications detailed above, may be due to the variation in response to the pH component of the burn.

In a preliminary test, it was found that a 30-percent reduction in score was effected by BAL and hyaluronidase mixtures when compared with BAL alone. However, since the standard error was large relative to the means, no significant difference was indicated.

It has been found that in the score range 0 to 20, the standard error approximated the mean score. Increasing scores to the range 30 to 60 alters this relationship since the standard error will generally increase proportionally less.

When standard error approximates the mean score, reasonable sample size will detect

TABLE 2
ESTIMATED SAMPLE SIZE NECESSARY TO GIVE THE SIGNIFICANT PERCENT CHANGE

Average Score BAL-treated Eyes	Standard Error of Each Mean	% Decrease in Score of BAL + Hyaluronidase-Treated Eyes (Compared to BAL-treated eyes)	Estimated Sample Size Necessary (To observe significant? [$\alpha=0.05$, $\beta=0.95$] changes)
20	14	75*	10*
30	14	33	26
		50	13
		66	7
40	14	25	26
		37	13
		50	7
50	14	20	26
		30	13
		40	7
		50	5

* In this case the minimum significant decrease ($\alpha=0.05$, $\beta=0.80$) was estimated from known sample size of 10.

only large differences. As the mean score increases in relation to standard error, smaller differences can be detected without using an impractical number of animals.

Table 2 shows the estimated sample size necessary to give the significant percent change ($\alpha = 0.05$ $B = 0.95$),⁷ if it exists, for each specified score for the control

(BAL-treated) eyes, when the standard error (S) = 14.

SUMMARY

1. Hyaluronidase has no effect on the severity of lewisite burns in the rabbit eye, and does not influence the treatment of these burns with BAL.

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CURARE AKINESIA IN CATARACT OPERATIONS*

JOHN W. HENDERSON, M.D.

Rochester, Minnesota

Although it has been known for some years that ptosis and diplopia were early manifestations of intoxication from curare, it has only been recently that such ocular difficulties were regarded as of any clinical importance.

On completion of the pharmacologic researches by McIntyre and co-workers,¹ in 1939, and Wintersteiner and Dutcher,² in 1943, the active principle of curare became available for clinical application. This brought about a change in the status of curare from a "curiosity poison" to an alkaloid that had therapeutic possibilities because its dosage could be controlled.

OPHTHALMIC USE OF CURARE

As an addition to medical therapeutics the drug was first used in a large series of cases by Bennett³ as an antispasmodic in individuals undergoing shock therapy with penty-

lenetetrazole (metrazole). Curare was next used in anesthesiology; the temporary muscular paralysis or akinesia produced by curare was widely utilized as an adjuvant to anesthesia. In the combined fields of anesthesiology and ophthalmology, mention is made of enucleation of an eye in a patient who was anesthetized by a mixture of curare and thiopental sodium in a report by Baird and associates,⁴ in 1948.

The first extensive study of the application of curare to an ophthalmologic problem appears to have been done by Kirby,⁵ in 1949. In this report, Kirby gave his personal impressions of the use of curare in certain selected cases in which the extraction of cataracts was required. He gave "relaxing" doses of curare to his patients and was favorably impressed with the ophthalmic akinesia that was produced.

Since Kirby's report, an increased interest in the ophthalmologic aspects of curare has been evidenced. The literature on this

*From the Section of Ophthalmology, Mayo Clinic.

subject, however, is still not large. Clark,⁶ Roche,⁷ Farquharson,⁸ and Cordes and Mullen⁹ have reported on the specific use of curare in operations for cataract.

Clark was of the opinion that use of this drug reduced the incidence of loss of vitreous in the 44 cases in which it was used. Roche determined that the minimal dose of curare required to perform intraocular operations in a group of 50 cases averaged 45 units (equivalent to about 6.7 mg. of d-tubocurarine chloride).

In Farquharson's series of 70 patients, curare was used as a supplementary drug to akinesia obtained by a combination of Van Lint infiltration and retrobulbar injections of two-percent solution of procaine containing epinephrine.

Cordes and Mullen, after using the drug in 85 cases, were so favorably impressed with its relaxing effect that they stated, "We are now coming to the conclusion that curare should be used in every case of cataract extraction."

More recently, Drucker, Sadove, and Unna¹⁰ carried out experiments with curare on normal volunteers. Notable among their findings was the fact that the extraocular muscles, as a group, were the last to recover from and the first to be affected by generalized akinesia induced by administration of curare.

In a still more recent report, Kirby¹¹ summarized his experiences over a five-year span with the administration of curare in nearly 600 patients undergoing operations for cataract. As the result of further experiences with this drug, Kirby is convinced that curare in combination with local anesthesia promotes the "expedition, delicacy, and precision" of removal of cataracts and is responsible for "the absence or diminution of complications, particularly of extrusion and loss of viscid vitreous."

My interest in the use of curare as an agent for the production of akinesia in cataract operations was stimulated by Kirby's initial report in 1949. As a result, it was de-

cided to administer curare to successive patients undergoing operations for cataract because it was deemed that a study of successive cases would supplement the knowledge already accumulated concerning the safety and behavior of curare in selected cases such as characterized Kirby's study.

METHODS

One hundred and thirty-eight successive operations for cataract, performed during 1950 and 1951, form the basis from which the data of this study were obtained. To be included in this study, it was required only that the patient be an adult and that an operation for cataract be required according to the usual indications.

Curare in the form of d-tubocurarine chloride (1.0 cc. of the preparation used throughout this study was equal to 3.0 mg. of d-tubocurarine chloride) was administered intravenously to all patients under the supervision of an anesthesiologist.

Curare was the sole agent employed for the purpose of akinesia; no local anesthetic agents were injected into any of the soft tissues of the eyeball or orbit or into the parotid plexus of the facial nerve. A 10-percent solution of cocaine was applied topically to the eye to induce anesthesia.

Secobarbital sodium (seconal) in doses of 1.5 gr. (0.1 gm.) was given preoperatively. Atropine, in doses of 1/150 of a grain (0.00043 gm.), was also administered preoperatively to combat the excessive secretion in the respiratory passages that sometimes occurs in patients receiving curare.

The intravenous administration of curare was commenced 10 minutes before the start of the operation. To allow such an interval for induction of akinesia permitted slower administration than if the drug was given in one injection just prior to the corneal section or preplacement of sutures. The anesthesiologist may use this interval of induction to observe the patient for any idiosyncrasies to the drug or undue respiratory distress such as might occur in a patient who

had latent myasthenia gravis, for example.

The rate of administration of curare was governed by close observation of the respiratory status of the patient and by a determination of the depth of akinesia at any given moment. To ascertain the latter, the patient was asked to perform some task that required muscular effort, such as squeezing the anesthesiologist's hand. Immediately prior to the operation, I examined the patient's ability to squeeze the eyelids and to rotate the eyes in various directions.

No operation was commenced until the muscular response of the patient to a command to look up was completely paralyzed or severely incapacitated. If insufficient curare had been administered in the 10-minute period of induction to bring about this degree of akinesia, the operation was delayed until the desirable degree was obtained.

The ages of these patients represented a reasonably good cross section of the age distribution among adults on whom operation for cataract is ordinarily performed. In 64 percent of the 138 operations, the patients were between 60 and 80 years of age. The youngest patient was aged 32 years and the oldest 92 years.

No attempt was made to select a type of cataract to be extracted under the plan of this study. In about 10 percent of the patients, the cataracts were of the type in which relatively poor surgical results might be anticipated from the standpoint of completion of the operation without accident or complication and from the standpoint of restoration of useful sight.

Included were cataracts that complicated such diseases as uveitis, cataracts associated with atrophy of the iris and posterior synechias, hypermature and morgagnian cataracts, those associated with secondary glaucoma, and cataracts extracted after previous operations for glaucoma.

RESULTS

Early in the course of the study, it was

found that some patients could not tolerate the curare as it was administered intravenously. Since one of the main objectives of this study was to evaluate the ability of curare to produce akinesia, the cases in which curare failed were carefully studied.

Any restlessness of the patient and any ocular movements during operation were considered to constitute poor akinesia. Any difficulty during the period of induction that made it impossible to proceed with the operation was also considered as unsatisfactory.

Results in the following cases were considered to be unsatisfactory:

REPORT OF CASES

Case 1. The patient was a 72-year-old woman; 4.0 cc. (12 mg.) of curare was given over a six-minute interval immediately preceding operation. The operation required 11 minutes.

Akinesia was unsatisfactory throughout the surgical procedure; respiratory distress was so pronounced that 0.5 mg. of neostigmine was given intravenously on completion of the operation.

Case 2. The patient was an 81-year-old woman; 3.0 cc. (9.0 mg.) of curare was given in a two-minute period.

Respiratory distress was so extensive that artificial respiration by forced oxygen pressure was required. When the patient was resuscitated, the operation was performed. Profound paresis of upward and downward rotation of the eyes and of the orbicularis oculi was present at the beginning of the operation.

Case 3. The patient was a 59-year-old woman; 5.0 cc. (15 mg.) of curare was administered in a period of five minutes. Good ocular akinesia was noted objectively, but the patient was apprehensive and restless.

Case 4. The patient was a 61-year-old man; 4.0 cc. (12 mg.) of curare was administered in a period of five minutes. So much respiratory distress developed that it was necessary to administer neostigmine and artificial respiration by forced oxygen. The surgical procedure was completed but loss of vitreous occurred.

Case 5. The patient was a 46-year-old woman; 3.0 cc. (9.0 mg.) of curare was administered in a period of five minutes. Great respiratory distress developed, but neostigmine or oxygen was not required.

Case 6. The patient was a 69-year-old woman; 2.5 cc. (7.5 mg.) of curare was administered, resulting in pronounced paresis of upward rotation of the eye and moderate paresis of downward rotation. No weakness of the orbicularis oculi was noted.

Objectively, the respirations appeared adequate but the patient complained so bitterly of inability

to get her breath that administration of curare was discontinued. The patient's speech did not seem to be affected.

A successful combined intracapsular extraction of the lens was then accomplished with the aid of an injection of procaine into the parotid plexus of the facial nerve (O'Brien's technique).

A second operation for cataract was performed almost a year later. Again, after administration of 2.5 cc. of curare, the patient experienced so much respiratory distress that administration of the drug was discontinued and the operation was completed with the patient under thiopental sodium anesthesia.

Case 7. The patient was a 68-year-old woman; 1.5 cc. (4.5 mg.) of curare was administered over a period of five minutes. So much respiratory difficulty developed that administration of the drug was discontinued and the operation was completed with the aid of injections of procaine hydrochloride into the retrobulbar space and parotid plexus of the facial nerve.

Case 8. The patient was a 77-year-old man; 3.0 cc. (9.0 mg.) of curare was administered over a period of nine minutes. Respiratory collapse occurred, and the patient was revived by administration of oxygen under pressure and of neostigmine.

The operation was completed with the aid of an injection of procaine into the retrobulbar space and the parotid plexus of the facial nerve. Preoperatively, the patient had been known to have atelectasis of one lung.

Case 9. The patient was a 61-year-old woman; 3.0 cc. (9.0 mg.) of curare was administered slowly during a period of 10 minutes. Respiratory distress threatened and pronounced paresis of upward rotation of the eye and moderate paresis of downward rotation were noted. No weakness of the orbicularis oculi was visible.

Akinesia was supplemented with an injection according to the technique of O'Brien. The patient was known to have asthmatic bronchitis.

Case 10. The patient was a 69-year-old woman; 4.0 cc. (12 mg.) of curare was administered. Akinesia was incomplete, for the patient moved the eye during the operation.

Case 11. The patient was a 54-year-old man; 5.0 cc. (15 mg.) of curare was administered, but the patient was still able to squeeze the eyelids and akinesia was considered to be incomplete.

Case 12. The patient was a 55-year-old woman; 4.0 cc. (12 mg.) of curare was administered, but akinesia of the eye and eyelids was incomplete.

Analysis of the data in these 13 instances of unsatisfactory akinesia involving 12 patients points to several explanations for the failure of this method. In the first five cases, it was considered that the patients received an overdose of curare. The drug was given either too rapidly or in too large an amount.

In three of these (Cases 1, 3, and 5), a

second operation for cataract was performed with successful results using intravenously administered curare. This would indicate that the unsatisfactory akinesia was not caused by any peculiarity on the part of the patient. In Cases 1 and 3, a smaller amount of curare was given at the second operation than at the first. In Case 5, the same amount of curare was given on both occasions, but it was given at a slower rate during the second operation.

In Cases 6 and 7, only small amounts of curare were administered yet difficulty occurred; these cases were classed as examples of undue sensitivity to the drug. Since flaccid paralysis was not extensive, it did not appear likely that latent myasthenia gravis was present in these instances. Perhaps the curare had some effect on the central nervous system in these individuals.

In Cases 8 and 9, the patients were known to have respiratory difficulty prior to ocular operation. Curare apparently greatly aggravated their respiratory embarrassment. In several other patients who had asthma, successful operation for cataract was carried out when curare was administered intravenously. However, in these latter cases the drug was given with great caution and even then the patients were on the verge of respiratory distress.

Cases 10, 11, and 12 apparently were examples of great tolerance to the drug. Satisfactory akinesia of ocular rotation could not be accomplished with the dosage used in these cases. The anesthesiologists were reluctant to give more than 12 to 15 mg. of curare in the period of induction. They considered that the safe limits of administration were exceeded when doses larger than 9.0 to 12 mg. (3.0 to 4.0 cc.) were given initially.

On many occasions, it was noted that the patients had a sense of suffocation or a feeling that they could not draw a breath during the period of induction. This phenomenon usually occurred even in the presence of adequate respiratory excursions.

It was considered that this sensation must

be produced by some effect of the curare on the central nervous system for, except in those cases listed previously, the difficulty disappeared when the patients were told that the drug was prone to produce such an effect and were assured that their respiratory status was satisfactory. Since this subjective distress did not interfere with the operation or cause restlessness on the part of the patient, it was not regarded as a manifestation of unsatisfactory akinesia.

Vitreous was lost during eight of the 138 operations (six percent). In two (Cases 3 and 4), it was considered that unsatisfactory akinesia was responsible for this loss, because of the restlessness of the patient. In the remaining six cases, other factors were responsible.

In an earlier paragraph it was pointed out that the operation was not commenced until a certain degree of akinesia of upward rotation of the eye was attained. Thirty-eight percent of the patients were considered to have pronounced weakness of upward rotation; in the remainder (62 percent), this function was completely lost in response to a command to look up.

It soon became evident that ability to look downward and to squeeze the eyelids was not affected as much as upward gaze. Although this difference was not great, there appeared to be less effect on the orbicularis oculi than on downward gaze. In only two patients was total simultaneous paresis of all three functions noted.

The amount of curare and the rate of administration required to bring about the desired degree of akinesia were quite variable. The smallest dosage required to bring about satisfactory akinesia was 2.0 cc. (6.0 mg.). In 66 percent of the cases, between 3.0 cc. (9.0 mg.) and 4.0 cc. (12 mg.) was required. The average for the entire group was 3.5 cc. (10.5 mg.). In six cases, more than 5.0 cc. (15 mg.) was given but in these instances it was necessary to supplement the initial satisfactory akinesia by additional small amounts of curare because of the length of the opera-

tion and the wearing away of the effect of curare.

The rate of administration was so altered by the respiratory status of the patient at any given moment that it was nearly impossible to formulate any set pattern by an analysis of the data. Administration of curare in the amount of 0.5 cc. per minute until the desired effect is attained would most closely approach the average experience in this study.

Although the degree of akinesia was not retested at the completion of the operation, the impression was garnered that the effect of an average dose (3.5 cc.) administered over a period of about seven minutes persisted for approximately 20 minutes at near maximal degree.

The effects would then subside in about 10 minutes, as determined by the ability of the patient to squeeze the examiner's hand. In general, 20 minutes of akinesia was usually adequate to permit completion of the operation and return of the patient to bed.

COMMENT

Many of the articles about clinical aspects of curare refer to its early effects on the eye. Results of this study tend to confirm this. The extraocular muscles appear to be among the first to exhibit the paralyzing effect of curare.

Not generally recognized, or at least not mentioned in the literature, is the fact that the sequence of paralysis induced by curare may be selective within the particular group of muscles concerned with ocular rotation. Thus, not all the skeletal muscles that control movements of the eye and eyelid are affected to a like degree.

This was demonstrated in this study by the fact that the ability of the eyes to rotate upward could be nearly paralyzed, yet the patient still retained some ability to look downward and to squeeze the eyelids. This was a most interesting finding; its possible explanation is intriguing.

It seems easiest to explain the differential

effect of curare on the function of ocular rotation in a vertical plane and squeezing of the eyelids on the basis of a sequence of paralysis of muscles innervated by different cranial nerves. The seventh cranial nerve, which innervates the orbicularis oculi, apparently was less affected by curare in the majority of patients than was the third cranial nerve and the muscles it innervates.

To explain the differential effect on upward and downward rotation of the eye on this basis is somewhat more difficult.

Since the function of looking upward is performed chiefly by muscles (superior rectus and inferior oblique) innervated by the third cranial nerve, whereas the function of looking downward also includes innervation from the fourth cranial nerve (superior oblique muscle), a selective effect of curare between adjacent cranial nerves might be postulated. If this is true, it attributes to curare a fine peripheral gradient effect that may not really exist.

Since the functions of upward and downward rotation of the eye were judged on the basis of response to command, the difference in response might be caused by some central effect of curare. On the basis of known pharmacologic facts, the former explanation is more plausible.

The tendency of the eyes to roll upward or the inability of the patient to look downward at some crucial moment during operation for cataract is one of the main bugaboos of surgeons who perform such operations. Because it nearly eliminates the ability of the eye to roll upward, curare should be a great boon to operative techniques for removal of cataract.

Lancaster,¹² as well as others, has spoken at various times of the importance of akinesia of the extraocular muscles; yet I and many others had considered proper akinesia of the eyelids to be a greater factor in reduction of the incidence of loss of vitreous.

As I have analyzed the results of this study and have watched many curarized patients attempt to squeeze the eyelids against

the speculum in the presence of a nearly immobile eye, I have changed my opinion as to the necessity of complete akinesia of the eyelids. Whenever the akinesia of the extraocular muscles was nearly complete, squeezing of the eyelids appeared to have little influence on the incidence of loss of vitreous.

At the beginning of this study, some question existed as to the selection of an ocular test that would properly reflect the degree of desired curarization. Since it was desirable to eliminate looking upward, this function was selected as one test of the degree of curarization. It proved to be a fortunate selection, for this function as a response to command could be nearly abolished.

It was thought that, if the patient was unable to roll the eye up even when coaxed or commanded to do so at the beginning of the operation, it was unlikely that this annoying movement would occur during the crucial moments before and after the delivery of the lens.

One of the puzzling features in this series of patients was a softening effect of the eyes that appeared evident clinically but was more difficult to prove objectively. The eyeball appeared more flaccid or to display loss of tonus in comparison to the eyes on which I had operated prior to this study. This softening effect has been noted by others.

At first, operation on these softened eyes appeared more difficult because a greater amount of traction on the lens and counter-pressure on the vitreous was required to bring about delivery of the lens. This apparently was a drawback to use of curare in operations for cataract but, as familiarity was attained with this diminished ocular tonus and with the altered mechanics of extraction, this difficulty was replaced by a feeling of security.

At completion of this study, it was concluded that surgical results were potentially better when the eye was softer. More varied manipulations can be carried out within reasonable limits on such eyes without fear of

loss of vitreous than can be done on the eyes of patients who have not been curarized.

On the basis of experience prior to this study, it was scarcely possible to maneuver a vectis inside the eye without fear of loss of vitreous. In this series, it was surprising to find that five cases occurred in which delivery of the lens was completed with the vectis without loss of vitreous.

In any evaluation of the practical application of curare to operations for cataract, it must be kept in mind that nearly paralyzing doses, so far as the extraocular muscles were concerned, were utilized in this study, whereas other investigators have recommended "relaxing" rather than paralyzing doses.

Farquharson, reporting on his series of 70 extractions of cataracts during which curare had been administered, found that it required between 20 and 60 units (3.0 to 9.0 mg. of d-tubocurarine chloride) with an average of 44 units (6.6 mg.).

These data agree closely with those noted by Roche, who found that 45 units of curare was the minimal dose necessary to obtain a quiet eye for intraocular operations. Such dosage is less than the average amount (10.5 mg. or 70 units) utilized in the study being reported. In 15 patients who did not have premedication, Roche found that the paralyzing dose was 76 units (11.4 mg. of d-tubocurarine chloride).

Although a paralyzing dose might not be deemed necessary, its use still appears to be practical since it was administered in 138 successive cases without undue complication. A smaller dose, such as permits only relaxation, might have but little more effect than the usually administered local anesthetics.

As already mentioned, the rate of administration of curare varied extensively in different patients and the rate was altered greatly according to the respiratory status of the patient at any moment; these variations make statistical analysis impossible. Nevertheless, the impression was gained that it was not the amount of drug given but rather

the rate of its injection that was the most important factor in safety.

This fact was learned chiefly by means of trial and error; had it been possible to apply the experience of the last half of the study to some of the initial patients, the incidence of cases of unsatisfactory akinesia probably would have been less.

As a rough guide to those who might try the drug, I propose that it be administered intravenously at a rate not to exceed 0.5 cc. (1.5 mg.) per minute after an initial injection of 1.0 cc. (3.0 mg.).

Contraindications to administration of curare to patients who have cataracts are few but definite. Even though several asthmatic patients were successfully operated on, patients who had difficulties in respiratory exchange were, as a whole, extremely hard to handle. I have discontinued administration of curare to any individual who has chronic bronchitis, atelectasis, bronchiectasis, asthma, or pneumothorax.

On the other hand, curare was given without complication to patients who had all varieties of cardiac and vascular difficulties. Such conditions as auricular fibrillation, severe hypertension, cardiac enlargement, generalized arteriosclerosis, angina pectoris, disease of the coronary arteries, and valvular cardiac disease did not prove to be contraindications to administration of curare.

One of the obvious drawbacks from a practical standpoint to use of curare in operations for cataract is the need for someone to supervise the injection of the solution. In this study, an anesthesiologist supervised this phase of the procedure; however, once an ophthalmologist becomes familiar with the use and behavior of curare anyone should be able to administer the drug intravenously under the direction of the ophthalmic surgeon.

Still, this need for another person to supervise administration of the drug is a factor that may prevent general utilization of this method of akinesia by ophthalmologists. Any procedure concerning surgical

technique in removal of cataracts that is not under direct control of the surgeon is a definite drawback in the opinion of many ophthalmologists.

Several publications concerning akinesia induced by curare include statements that a discussion of antidotes has no place because, if the drug is administered correctly, no need for antagonists of curare exists. No matter how skillfully a drug may be administered, instances of undue sensitivity to even small amounts will be encountered when it is given to a large enough group of patients.

In this study one patient experienced respiratory embarrassment after receiving 1.5 cc. (4.5 mg.); in several patients, it seemed advisable to administer neostigmine. The neostigmine was given in conjunction with artificial respiration by means of positive pressure. Until recently, neostigmine was the drug most widely used as an antagonist of curare, although from a pharmacologic standpoint it was known to have several drawbacks as to its specificity and reliability for such purpose.

Now a commercial preparation, N-ethyl-N-(m-hydroxyphenyl)-N,N-dimethylam-

monium bromide (tensilon), is available that, by preliminary clinical trial, appears to have a more specific and faster effect against paralysis of peripheral muscles than any other drug at present. Although it has not been necessary to use tensilon in this study, it is another safety factor that insures safer use of curare and is of reassurance to the surgeon in time of need.

Although this study was begun with some skepticism as to the practical value of curare as an aid to akinesia during operation for cataract, it is now considered that the drug is of great help in this particular phase of ophthalmology. Since the conclusion of this study, I have continued to use curare in all extractions of cataracts except when the drug is contraindicated.

Lancaster,¹² in a paper on operation for cataract, once said, "My aim is to receive a patient who cannot feel, does not want to move, and could not move if he tried." Curare bids fair to solve the third factor of Lancaster's dictum for the successful preparation of patients who are to undergo removal of cataracts.

The Mayo Clinic.

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THE PRESENT TECHNIQUE AND RESULTS OF THE USE OF CURARE IN OCULAR SURGERY

J. I. BARRAQUER MONER, M.D.
Barcelona, Spain

In this paper, I have summarized that which I have reported in former publications, and I have added the modifications suggested by our experience in the latest 500 cases of ocular surgery in which curare was used.

Employing the technique of Kirby,¹ I began to employ d-tubocurarine-chloride in ocular surgery in June, 1949; I used this akinesthetic at the beginning in a sporadic manner, applying it only in those cases in which I foresaw complications, either of a local or of a general kind, which seemed to indicate its use. Later on, I used it systematically with local anesthesia as the only akinesthetic in all intraocular surgical interventions.

In October, 1949,² I published the results of the first 116 cases and explained, at the same time, the evolutionary process of my ideas and concept of the indications and technique of administration, taking Kirby's method as the starting-point, right up to the use of curare as the only akinesthetic, with anesthesia consisting of simple instillation of a cocaine-adrenalin solution.

In 1950,³ after observing 516 applications of curare, I arrived at the following conclusions:

1. Curarine is an effective help in intraocular surgery.
2. No important accidents can happen when the necessary precautions are taken.
3. It allows intraocular manipulations that would not be possible if local akinesia

EDITOR'S NOTE: It must not be assumed by the reader that the approach to general akinesia and the use of curare can be made in a casual manner even though the evidence is mounting that curare akinesia yields results which may not be achieved otherwise. The reader is urged to study the cautions dealt with in the articles on curare by Kirby and others.

were employed.

4. It controls passive uveal congestion.
5. It spares the patient the side effects caused by local akinesia.

In 1951, I reported 1,000 cases⁴ and described the technique of administration, which had been perfected with the help of Escuin Vera.⁵

EARLIER TECHNIQUE

This technique was described as follows:

Previous preparation of the patient was the same as is routinely done, then curare was injected intravenously at the rate of 2.5 to 3.0 mg. in the course of the first minute. After administering this dose, I waited for a minute, during which I observed the ocular signs of the progress of the curarization. The injection was then continued at the rate of one mg. per minute until I obtained a deep sigh, which, according to Escuin, may be interpreted as a loss of diaphragmatic tonus, or until palpebral ptosis set in, indicating the beginning of the paralytic phase.

Before I began the operation, I waited for another two minutes to make sure that the drug had reached its highest effect.

I encountered no serious accidents in any of these cases and only in approximately three to five percent did I observe a beginning of anoxia, which made the use of prostigmin (0.25 to 0.5 mg.) necessary for half the number of these cases, and which in no case prevented me from carrying out the surgical intervention in a normal manner.

ACTUAL TECHNIQUE (1952)

During the second half of 1951, Dr. Marten-Ellis thought that the occasional or rare cases of anoxia that I had observed were due to the initial dose of 2.5 to 3.0 mg. of

curare being injected in the course of the first minute and advised me to carry out the injection from the beginning at a rate of one milligram per minute, until the desired degree of muscular atony was reached.

The actual technique is, therefore, identical to the one described in 1951 so far as preparation and anesthesia of the patient are concerned. The only change consists in a modification of the administration rate of curare, which has been fixed at one milligram per minute from the beginning of the curarization.

With this technique the doses of the drug administered are considerably higher (about 1.0 or 2.0 mg. more). The number of cases in which there is any sensation of anoxia has decreased remarkably, to less than three percent (according to the series).

The needle is left in its intravenous position during all the operation in order that small doses of the drug may be injected in case the operation is drawn out or if it becomes necessary to obtain a deeper akinesia at a certain moment.

DOSAGE

The doses which have been necessary range between 3.0 to 25 mg., according to the patient's condition and to the time needed for the operation.

There is no fixed dosage in the use of curarine. This is an individual problem which is governed by the degree of atony necessary to carry out the intervention. The drug is always injected intravenously and at the rate of one milligram per minute.

DURATION OF THE AKINESIA

Once a satisfactory degree of akinesia has been obtained, muscular hypotony lasts for about 15 minutes after the administration of the drug has been interrupted. The akinesia may be drawn out for more than an hour, if necessary, by injecting fractions of a milligram during this time, the akinesist being guided herein by the symptoms that will be described later on.

NORMALIZATION OF THE TONUS

The patient's recovery is spontaneous and fast; the systematic use of prostigmin after the operation is not necessary and should be formally outlawed; it is a possible cause of physical uneasiness for the patient and also prevents one from taking full advantage of his technique. The persistence of a certain degree of akinesia during the patient's transport from the operating room to his bed, and of a certain relaxation during the first minutes of the postoperative period, are both excellent means to prevent postoperative complications.

In some recent cases, I have injected 30 to 60 mg. of an oily solution of d-tubocurarine-chloride intramuscularly toward the end of the operation, in order to make the postoperative atony last longer, but my experience (although favorable) is still not sufficient to allow me to arrive at any definite conclusions.

RELAXING ACTION OF D-TUBOCURARINE

The main pharmacologic action of curare is of a muscle-relaxing nature, with a predilection for the periocular muscles, which are first affected.

The progress of curarization is characterized mainly by the disappearance of muscular tonus and then, as the dose is increased, by atonic paralysis (Rijlant).⁶

The ocular-surgical phase lies between the disappearance of muscular tonus and the appearance of the first paralysis (ptosis), although it is generally not necessary to go this far. Later, a systematic disappearance of the tonus of all the muscles of the body is observed, which gives the patient a feeling of relaxation. This is very favorable for complete physical rest which, in turn, produces psychic rest. Atony of the muscles of the various parts of the body, of the tonus, and of the abdominal wall are the cause for the decrease of venous tension, one of the main advantages of curarization, which until now could not be obtained with any

other method permitting the use of local anesthesia.

Manometric measurements carried out with the manometer of Lester Cohen have shown that the venous tension in the vena mediana is reduced to approximately 50 percent of its value at the beginning with the dosage I employ in ocular surgery.

As a consequence of the disappearance of the tonus and of the paresis of the periocular muscles, local akinesia, which is so very necessary in intraocular surgery, is obtained.

As a consequence of the decrease of the venous pressure, an orbital and choroidal depletion occur and produce a certain irreversible degree of hypotension that is maintained as long as the drug has its effect. By putting the patient in a slightly slanting position (head higher than feet), a greater depletion of the cephalic vein is obtained.

D-tubocurarine-chloride does not act upon the irido-ciliary muscles, a fact that has been recently checked by Luelmo,⁷ who experimented with auto-injections of curare.

Although the drug has no direct effect on the pupil, the orbital venous depletion, with the accompanying strong hypotension, brings on a behavior of the pupil that, on first sight, might be considered paradoxical. In fact, the anterior chamber of a curarized eye is opened and when the aqueous humor flows out, the pupil dilates instead of contracts.

This fact may be easily explained when it is taken into account that the cocaine-adrenalin, employed for anesthesia, has not yet taken a sufficiently full effect to provoke mydriasis, but causes the dilatation of the pupil after the incision.

On opening the anterior chamber of a non-curarized eye, the crystalline lens moves a little bit forward, thereby increasing the tension on the iris, which reacts by contracting the pupil. If we take, on the other hand, a curarized patient and open the anterior chamber, the crystalline lens moves backward, leaving the iris floating in the anterior chamber; the cocaine and adrenalin may then exercise their mydriatic effects.

It is in this way then that curarization, by causing the disappearance of the tonus, as well as by producing paresis of the periocular muscles and decrease in venous tension, brings such a degree of quietude and steadiness to the ocular globe as could never be obtained by the effects of local akinesia alone (retrobulbar, facial akinesia, and so forth).

TECHNIQUE OF ADMINISTRATION (1952)

With the following technique, I have already gathered experience in some 500 cases (bringing the total number to 1,500. I had previously reported 1,000 cases).

On the night before the intervention a regulator of the neurovegetative system is given (for example, two tablets of Bellergal—one tablet of Bellergal contains 0.0001 gm. of belladonna-alkaloid, 0.0003 gm. of ergotamine, 0.02 gm. of luminal [phenobarbital]), followed by a soporific drug (for example, 0.10 gm. of nembutal or luminal). This dose is repeated on the following morning, two hours and one hour before the operation.

In the case of nervous patients, the dose of the soporific drug should be increased accordingly and patients affected by any bronchial secretion should be given one half to one mg. of atropine sulfate by subcutaneous or intramuscular injection.

Fifteen minutes before operation, when the patient is already in the anteroom of the operating room, an adrenalized four-percent solution of cocaine is dropped into both eyes every three minutes. At the same time, while the aseptis of the eyelids is being carried out, the fornices of the conjunctival sacs are irrigated and drugs acting on the pupil are instilled, when and if necessary.

Once the patient is inside the operating room, the cocaine solution, hitherto given in a four-percent solution, is employed in a more concentrated solution (six to 10 percent), which is instilled into the eye to be operated at the same interval as before, until

the moment the operation is begun, that is, 10 to 12 minutes later. At the same time, intravenous injection of curare is begun.

In cases in which several operations on the iris have to be performed, as well as in those in which I suspect the zonule to be resistant, also when the globe is inflamed or when the ocular tension is high, the anesthesia should be made more intense by a subconjunctival or retrobulbar injection of novocain.

To carry out the injection of curare intravenously, syringes with a graduated, magnified scale, like those used for insulin, are very useful, as they permit an exact control of the dosage.

Ten mg. of curare in solution are now drawn up into the syringe, the needle is inserted in the v. mediana and then fixed in its position by a band of adhesive tape; the same should be done with the syringe.

The injection is then carried out at the rate of *one milligram per minute*, until the required depth of akinesia is reached. As soon as this moment arrives, the intervention may be begun. (Couadau and Campan⁸ are of the same opinion). The needle should remain in place during the whole operation in case it should become necessary to administer more curare.

The administration of oxygen in an open circuit is recommended to compensate for the respiratory deficiency. The easiest way of giving it consists in connecting a rubber tube to the oxygen container and fixing the tube with a pair of pincers to the sheet covering the operative field, the tube opening being under the sheet, which is thus used as a tent. An adequate rate of oxygen administration is 12 liters a minute.

Oxygen administration is not absolutely necessary, but now that I have begun using it, I go on doing so. It is recommended even in cases without curarization to alleviate the purely subjective reactions caused by the closure of the operating field.

In hyperemotional patients who come to the operating room before the necessary de-

gree of sedation has been obtained, I recommend giving a barbiturate intravenously or, if there is no barbiturate, some morphine or a substitute of the demerol type, which, in my experience, if it has been manufactured recently and is given with a syringe which is not warm, does not produce any postoperative vomiting.

SIGNS IN SURGICAL CURARIZATION

Both surgeon and akinessthetist may at any given moment observe the degree of curarization in the patient without interfering with each other, the former judging it by the ocular, the latter by the respiratory symptoms and signs; the greatest attention should be given to the latter.

A. OCULAR SYMPTOMS

1. Higher degree of mobility of the globe in the orbit as tested by moving the globe with the blunt end of any instrument.

2. Nystagmoid movements are tested by ordering the patient to look in this or that direction. The first muscle to be affected is the internal rectus.

3. Paresis of the orbicularis muscle of the eyelids is tested by pulling at the upper eyelid with an elevator, the suppression of the tonus being so evident that no confusion is possible.

4. Ptosis is tested by ordering the patient to keep both eyes open and to look up. The appearance of ptosis indicates the upper limit of curarization that should be obtained. It is, however, unnecessary to reach this point to have satisfactory akinesia.

B. RESPIRATORY SYMPTOMS

The interpretation of these has been subject to several changes according to the modification of the administration technique.

1. Cessation of intercostal respiration is tested by simple observation or palpation.

2. Modifications of the diaphragmatic rhythm.

The respiratory rhythm is frequently irregular at the beginning of curarization.

When the costal respiration disappears, the diaphragmatic action goes on but is somewhat irregular in depth as well as in frequency. It becomes normal as the drug takes its effect.

Regularity of both frequency and depth of the diaphragmatic movements indicates that the moment for the surgical phase has come. Decrease of the depth of regulator diaphragmatic movements indicates that administration of the drug should be interrupted; increase of depth indicates that it is time to inject another milligram of curare but not more than one mg. per minute.

The akinesthetist may thus, by simple observation of the diaphragmatic movements, adapt the akinesia to the surgical stage without hindering the surgeon in his work. (The diaphragmatic movements are determined by simple observation through the sheets that cover the patient or by palpation of the epigastric region.)

RESULTS OF GENERAL AKINESIA

The direct results of the excellent akinesia and hypotension produced by curare are:

1. Simplification of all operative manipulations.

2. Decrease in the number of accidents. All operative accidents show a decrease in frequency and seriousness, especially in the losses of vitreous which, when local akinesia was used, amounted to four to six percent, and which, with curare, have been brought down to one to two percent. In several series of 100 cases each, there has not been even a single slight hyaloid rupture.

Curarization appears to be the most efficient way to safeguard against an expulsive

hemorrhage, a complication once faced with a feeling of helplessness.

INDICATIONS

In all intraocular interventions—cataract extraction, antiglaucoma interventions, keratoplasty (whether penetrating or not)—and in removing corneal or of corneoscleral sutures in uncoöperative patients, curare akinesia is indicated.

There are no contraindications to using curare in the same patient several times within a few successive days, and we have even done it twice on the same day.

PRECAUTIONS

In addition to those patients who suffer from myasthenia, the ones who are overweight and who have a short and fat neck are those who require the utmost care. In two cases, I have observed anoxia before the surgical stage of akinesia was reached. It was then necessary to resort to general anesthesia with sodium-pentothal.

Physical weakness does not seem to be a contraindication; these patients behave and recover perfectly well but usually require a smaller dosage.

CONCLUSION

It seems evident that general akinesia, as produced by curare with local anesthesia, has made possible real advances in ophthalmic surgical technique and is capable of producing better results in all interventions on the ocular globe.

Experiences with my modified methods of administration are in agreement with those of Kirby.⁹

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VISUAL SKILLS AND THEIR RELATION TO SCHOOL ACHIEVEMENT*

NEWELL C. KEPHART, PH.D.

Lafayette, Indiana

For a number of years the Occupational Research Center at Purdue University has been interested in the problem of the relationship of visual skill test scores to success in the performance of industrial jobs. Studies in this field have resulted in the analysis of well over a million visual skill tests of industrial employees.

Recently, much interest has developed in the study of similar problems and relationships among children in schools. Our philosophy has been to approach the problem in the school situation in much the same manner in which we approached it in the industrial situation.

The school child can be thought of as being engaged in a task which is not dissimilar in many respects to the task in which the industrial worker is engaged. The similarity is perhaps most striking when we compare the school task with that of the clerical worker in industry. Following this line of reasoning we decided to consider school work as another example of a job and to treat visual tests of school children in exactly the same manner as we had previously treated visual tests of industrial employees.

The first facet of the problem involved the question of the distribution of vision test scores among the school population. Is the visual skill level among school children generally higher or lower than that in an

industrial population? Is the frequency of children, whose test scores would indicate that their vision is not adequate for their task, great enough to warrant extensive study?

As a beginning on the study of this facet of the problem, 2,200 school children in grades three through 12 were given a battery of visual skills tests. This battery was that incorporated in the Ortho-Rater,[†] an instrument which has been widely used in the testing of industrial employees.

The Ortho-Rater battery includes tests of 12 visual skills. At a distance optically equivalent to 26 feet, tests are included for vertical and lateral phoria, acuity of both eyes, right eye alone and left eye alone, depth perception, and color discrimination. At a distance optically equivalent to 13 inches, tests are included for acuity of both eyes and of each eye separately, vertical and lateral phoria.

Distributions were made of the test scores of these school children for each of the 12 tests in the battery. These distributions were then compared with similar distributions of scores made by 7,655 industrial employees.

This comparison indicated that in each of the tests, the distribution of scores of school children was strikingly similar to that

* From the Division of Education and Applied Psychology, Purdue University.

† The Ortho-Rater is a visual testing instrument manufactured by the Bausch & Lomb Optical Company, Rochester, New York, for the visual classification and placement of industrial employees.

of scores from industrial workers. This would indicate that the proportion of school children whose vision-test scores are below standard is as great as the proportion of industrial workers whose scores are below standard.

The binocular acuity tests will serve to illustrate these results. Figure 1 shows the distribution of scores made by the two groups on the binocular far acuity test. These are cumulative percentage curves.

Along the base line are the scores on the acuity test (the Ortho-Rater acuity tests have 15 steps). Along the vertical axis are indicated the percent of individuals scoring at or below each of the indicated score levels.

It will be seen from Figure 1 that the curves for the two groups tested are very close together. There is no evidence of a significant difference between the two groups. If anything, the school group is just slightly lower than the industrial group. However, as we have stated, this is not a significant difference. These curves do indicate that the frequency of lowered far-acuity scores is as great among the school children as it is among the industrial population.

Figure 2 shows the two similar curves for scores on the binocular near-acuity test. We frequently think of low near acuity

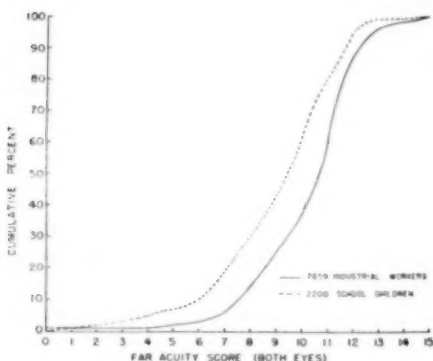


Fig. 1 (Kephart). Distribution of scores on binocular far-acuity test of school children compared with that of industrial employees.

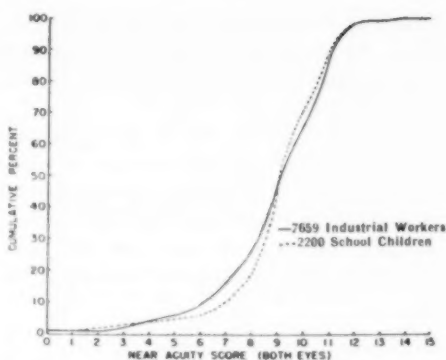


Fig. 2 (Kephart). Distribution of scores on binocular near-acuity test of school children compared with that of industrial employees.

scores as being primarily a phenomenon of the older age groups. We think of middle age and the onset of presbyopia when near acuity difficulties are mentioned. This figure shows quite strikingly that this is not the case and that, in fact, there are as many children with low near-acuity scores as there are adults in the industrial population with low near-acuity scores.

In this near-acuity chart, the curves from the two groups are almost exactly identical indicating that the distributions of such scores are identical and that difficulties arising from low near-acuity scores are as frequent in children as they are in adults.

These near-acuity scores are of particular interest in the school situation since the school task is essentially a near-point task. Beginning at about the fifth grade and continuing throughout the remainder of his school career, the child is required to spend a major portion of his time in critical near-point seeing.

He must read large quantities of material, not as he did in the first three grades, to develop the reading skill itself, but to gather rapidly and accurately the content of the printed page. He finds that he must write more and more material and must analyze diagrams and drawings. As a matter of fact, we find a characteristic change in the child's visual adjustment corresponding to this

fourth or fifth grade level where he completes the development of the educational tools and begins to use these tools to further his knowledge.¹

Thus from grade five to grade 12, the child experiences an environment in which the near-vision skills become increasingly important. As we see from this figure, he is no better equipped to cope with this near-point task than is the adult industrial employee.

Nor does the customary visual test, so frequently administered in schools, give us much help in identifying those children who have lowered near-point skills. The test most frequently used is the Snellen chart. The test is a letter chart designed to be administered at a distance of 20 feet. As such, it measures far-point skills only.

Tiffin,² Giese,³ and others have pointed out statistically, and clinical practice has indicated repeatedly, that the relationship between far-acuity scores and near-acuity scores is very low in the adult population. Knowledge of an individual's far-acuity scores helps us very little in determining his ability at the near point. What is true of the adult population is also true of the school child population.

In a study of 2,181 test scores of school children, the correlation between binocular acuity scores at the far point and binocular acuity scores at the near point was found to be 0.55. This coefficient is sufficiently high to indicate that a relationship does exist between tests at the two distances. It is not, however, high enough to permit prediction of one ability from the other.

If we knew the distance score, our estimate of the near score would be improved by 16 percent over a "best guess." In other words, if we merely guessed the near-point score, we could improve our accuracy only 16 percent by having knowledge of the far-point scores.

Among these 2,181 school children, there were 541 who were below standard in near acuity. Of this number, 42 percent were

above standard at the far point. If only a far-point test were administered, this latter group would not have been identified. In other words, 42 percent of the children who need help will be passed over and given no attention if only the customary far-point test is administered.

School work is primarily a near-point task and, therefore, near-point visual skills assume greater importance. Since a far-point test will not adequately predict near-point ability, it follows that any visual test for use with school children must include tests at the near distance.

The importance of the problem of visual skills in the industrial situation has been recognized for some time. It has been agreed that the number of industrial employees whose visual skills are below the requirements of the job on which they are employed is of sufficient magnitude to constitute a major area in which help should be made available. From the figures just mentioned we can conclude that the problem among school children is of equal magnitude.

Numerous studies of industrial employees whose scores are below minimum standards for their job has revealed that between 40 and 50 percent of the industrial population is visually handicapped on their jobs. One study of 2,420 industrial employees gave 47 percent whose scores were below standard. When one of the same minimum standards (clerical and administrative) was applied to the test scores of 6,223 school children, 50 percent of the children had scores which were below the standard. Here, again, we see how similar the problem is in the two groups.

Approximately half of the children in our school systems are visually poorly equipped for their tasks. Surely this is a large enough percentage to constitute a very real challenge to both educators and the ophthalmic profession.

Of most immediate concern to the educator, however, is the problem of increasing the achievement level of the child in the

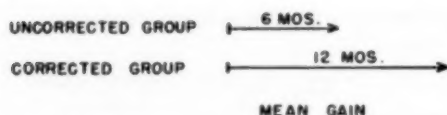


Fig. 5 (Kephart). Effect of professional assistance with visual skills on school achievement.

those students who did not meet the visual standards, however, only 28 percent were above their grade average in reading achievement. The difference in percent of the group above grade average in achievement was 18 percent in favor of the group who met the visual standards. This difference has a *t*-value of 2.92 and is therefore statistically significant. This is one example of the relationship which exists between visual test scores and school achievement.

A similar example is shown in a study of 468 seventh grade children in a school system in Virginia. In this study, the teachers were asked to rank their pupils in terms of overall school achievement. These rankings were used as the criterion. The school achievement profile was then used to determine the visual skill status of each pupil.

Among those pupils whose vision was adequate, 56 percent were in the upper half of their classes as rated by their teachers. Among those students whose vision was not adequate, however, only 47 percent were in the upper half of their classes as rated by their teachers. The difference in percent between the two visual test groups (nine percent) was statistically significant, the *t*-value being 3.06.

A slightly different approach to this problem was taken in a study performed at the Colorado Industrial School for Boys.⁴ All boys in this institution were tested with the Ortho-Rater battery.

From those boys who, the survey showed, had visual skills which were not adequate to the school task, two groups were chosen. These two groups were so chosen that they were matched in IQ and educational achievement, as measured by the Stanford battery, at the time of the survey. All boys in both

groups were in need of help with their vision.

The first group, composed of 25 boys, was given a complete refraction by a qualified optometrist and whatever help was needed was given them (glasses, visual training, and so forth). The second group, composed of 27 boys, was also given a complete refraction by the optometrist and was treated in exactly the same way as the first group except that the corrective measures which they needed were not given.

At the end of a four-month period, both groups were administered the Stanford battery a second time. It was found (fig. 5) that the group which had received the corrective measures had increased their educational standing 1.2 years. The control group which had not received these corrective measures had increased their educational standing only 0.6 years. The corrected group had progressed twice as fast as the uncorrected group.

This difference in rate of progress was statistically significant, the *t*-value being 4.92. It was concluded from this study that improvement of visual skills through professional assistance leads to more rapid progress in achievement.

It is felt that the series of studies which we have discussed lead to the following conclusions:

1. A significantly large number of school children have visual skills which are below the levels required for efficient performance of their tasks.
2. The nature of the distribution of visual skill test scores among school children is not materially different from that found in an adult industrial population.
3. A relationship can be demonstrated between the visual skill status of school children and their academic achievement.
4. The improvement of visual skills through professional attention leads to more rapid progress in school achievement.

Occupational Research Center.

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EXAMINATION OF THE CORNEA WITH THE
PHASE-CONTRAST MICROSCOPE*

J. FRANÇOIS, M.D., AND M. RABAEY, M.D.
Ghent, Belgium

Up to the present time very little work has been done on the histologic and histopathologic examination of the different ocular tissues with the aid of the phase-contrast microscope. In addition to our personal studies on the lens and on the corneal dystrophy in Hurler's disease, there is only the work of Schwarz and Schuchardt on the vitreous body.

The use of the phase-contrast microscope is indicated for the examination *in vivo* of the ocular tissues and in particular of certain layers of cells—for example, the lens capsule, the corneal endothelium, or the pigmentary epithelium—which can be isolated after fine dissection. It permits with a surprising clarity the demonstration of structural details, which the normal histologic methods are incapable of showing.

To be convinced of the advantages of this method of investigation, it is only necessary to remember the difficulties which were encountered by Yap Kie Tiong (Utrecht) during the course of his studies on the corneal endothelium in connection with corneal grafting. After having described his unsuccessful efforts to render visible the endo-

thelium in fresh corneas, the author concludes: "After all these fruitless attempts to obtain a picture of the endothelial cells, I was forced to conclude that no such picture exists." We shall see shortly it is possible to obtain very good pictures, thanks to the phase-contrast microscope.

The fact that these reveal, without artifice, the true architectural structure of the refracting media of the eye, is so important because the transparency of these media depends to a great extent on this structure. But the ordinary histologic method shows us only the true architectural structure of refracting with the tissue substances, or after their diffuse absorption by the preparation. The real structural aspect is often to a great extent invisible or obscured.

To illustrate these facts we will be able, with the aid of several photographs, to de-



Fig. 1 (François and Rabaey). Isolated epithelial cells. (Left) Two superficial cells; objective 40, ocular $\times 10$. (Right) A basal cell; objective 85, oil immersion, ocular $\times 10$.

* From the Ophthalmological Clinic of The University of Ghent. Supported in part by a grant from the Belgian Fund for Scientific Research. The phase-contrast microscope used for these investigations was made by Wild and Company, Heerbrugg, Switzerland. It is supplied with four "phase" objectives (Ph 7/0.20; Ph 20/0.45; Ph 40/0.66; Ph 85/1.25 immersion), and three oculars (5 \times , 7 \times , and 10 \times).

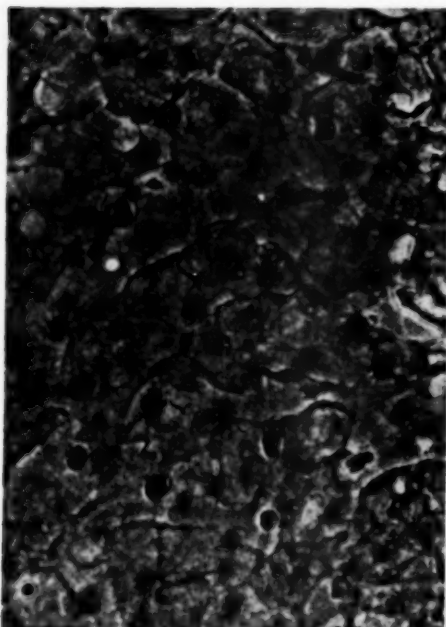


Fig. 2 (François and Rabaey). Epithelial cells. Objective 85, oil immersion, ocular $\times 10$.

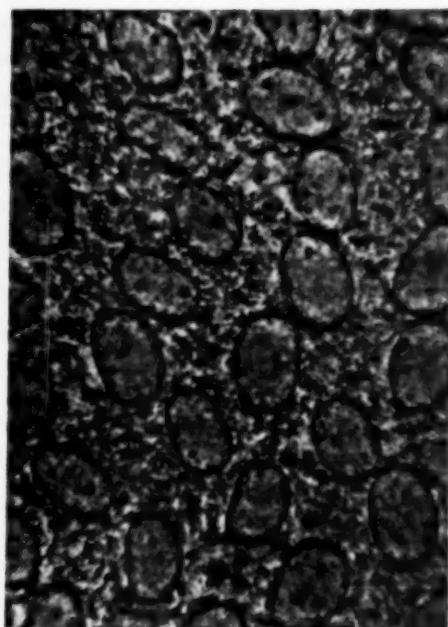


Fig. 4 (François and Rabaey). Endothelial cells. Objective 85, oil immersion, ocular $\times 10$.

scribe the essential characteristics of the different parts of the cornea, which are revealed to us by examination with the phase-contrast microscope.

After abrasion, the epithelial cells can be examined easily in isotonic serum. Figure 1 shows the aspect of isolated cells, superficial

and deep; the disposition of the cytoplasmic granulations is clearly visible.

It is, meanwhile, more interesting to examine a compact group of epithelial cells, in order to be able to study their reciprocal connection and disposition. Figure 2 demonstrates very well this point of view.

It is not possible to separate Bowman's membrane and that of Descemet from the corneal stroma. In section, these membranes are homogeneous. The anterior surface of the cornea, after removal of the epithelium, is not, however, completely smooth. Figure 3 shows a polystyrene reproduction of this surface; a structure in mosaic, due to the implantation of the basal cells, is clearly visible. This structure probably is not due to Bowman's membrane but to the basal membrane of the epithelium. The view of Descemet's membrane after abrasion of the endothelium shows no structure.

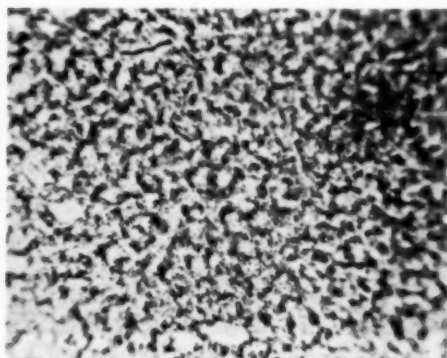


Fig. 3 (François and Rabaey). Polystyrene reproduction of Bowman's membrane. Objective 40, ocular $\times 10$.

The best picture is given by the endothelium. This consists of a very fine cellular

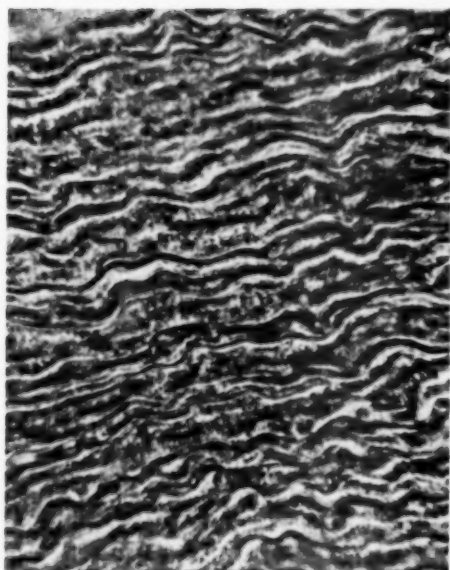


Fig. 5 (François and Rabaey). Corneal stroma suspended in water. Objective 85, oil immersion, ocular $\times 10$.

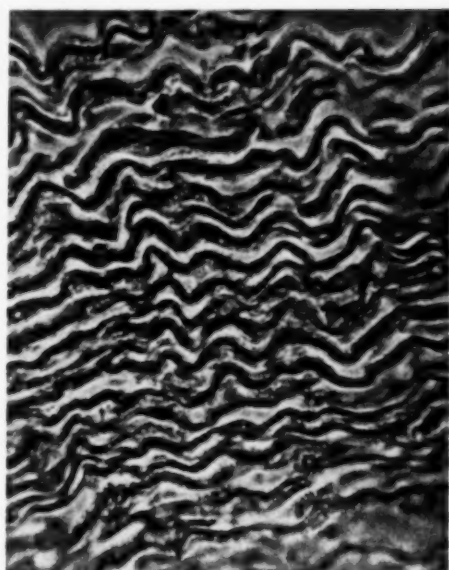


Fig. 6 (François and Rabaey). Corneal stroma suspended in water. Objective 85, oil immersion, ocular $\times 10$.

layer which permits good contrast, even at great magnification. Figure 4 shows the endothelial cells suspended in the aqueous humor and examined with the immersion objective. After focusing on the nuclei, it is seen that the latter contain, generally, two nucleoles, and that their wall is clearly visible.

The cytoplasm contains an astonishing quantity of granulations of a variable volume, which constitutes the proof of an intense cellular activity. The impression is given that this cytoplasm forms a syncytium, but it is possible to see very easily the limits of the cells when focusing on the superficial cellular parts.

The corneal stroma has been examined in section after fixation by formol and inclusion in paraffin. Figures 5 and 6 show the picture of an unstained preparation, very finely cut (2.0μ) and suspended in water. The regular disposition of the conjunctival lamellae is very clear.

It is, on the other hand, remarkable to

find that the image is completely different when examining a preparation mounted in Canada balsam or in clarite (fig. 7). With this mounting material, it is necessary that the section should be sufficiently thick (5.0μ), if a sufficient contrast is to be obtained.

A fine, rather irregular network is seen, resembling that which gives a coagulated

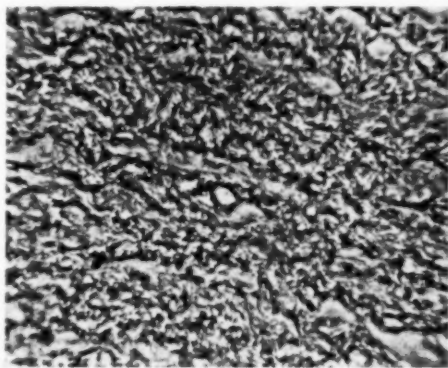


Fig. 7 (François and Rabaey). Corneal stroma mounted in Canada balsam. Objective 85, oil immersion, ocular $\times 10$.

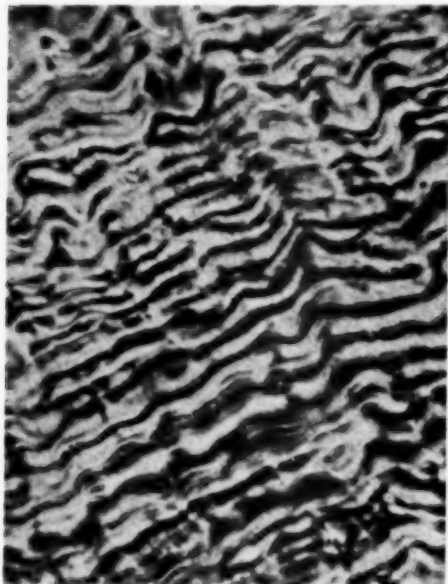


Fig. 8 (François and Rabaey). Polystyrene reproduction of the corneal stroma. Objective 85, oil immersion, ocular $\times 10$.

muciform mass. This aspect recalls that which is seen with an ordinary microscope in the preparations in which the corneal mucoid has been selectively colored by methylene blue or toluidine blue.

These observations show well, it seems, that the refracting properties of the different parts of the corneal stroma are of such a nature that the examination by the phase-contrast microscope of a preparation suspended in water shows principally the conjunctival lamellae, whereas the same preparation mounted in Canada balsam or clarite shows the mucoid instead.

At this point, it is necessary to point out that the contrast in a given preparation depends on the difference in refraction properties which exists between this preparation and the mounting material. If there is no difference, the preparation will be invisible.

On the other hand, by using mounting materials with a variable index of refraction, the contrast can be modified and augmented so as to obtain the maximum visibility for a given preparation and even, in the same preparation, for its different constituents.

If, therefore, the preparation under examination is composed of two constituents of a different index of refraction, it is possible, by changing the mounting material, to give a maximum contrast and visibility to one of the constituents, while the other becomes invisible. Taking the corneal stroma, for example, one should be able in that way to render the collagen and the mucoid selectively and separately visible.

If, in addition, the thickness of the diffraction plate, contained in certain objectives of the phase-contrast microscope, is decreased, as well as the size of the corresponding ring which is found in the condenser, the half-tones are shaded out in such a way as to obtain a narrow zone of maximum contrast, which permits a yet more minute differentiation of the constituents of the preparation.

In conclusion, another figure, a polystyrene reproduction of the corneal stroma (fig. 8), is presented. It resembles the negative image shown in Figure 6.

2 Avenue Pasteur.

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CLINICO-PATHOLOGY OF OCULAR FOREIGN BODIES*

BERNARD A. ROBERTS, M.D., AND ABRAHAM SCHLOSSMAN, M.D.

New York

In this era of great industrialization the ophthalmologist faces the problem of dealing with a wide variety of intraocular foreign bodies. However, by the use of safety devices the number of accidents has been considerably reduced, and we do not obtain as many specimens as heretofore. With the possibility of total warfare ever lurking in the background, it is conceivable that the number of intraocular foreign bodies which the ophthalmologist must treat will increase. During World War II, retained foreign bodies were found in 731 of 3,882 enucleated eyes of soldiers examined at the Army Institute of Pathology.¹

One way of studying reactions of foreign bodies is to expose animal eyes to various agents; but animal tissue reactions are not always analogous to those of humans. Therefore we felt that we could obtain a truer picture of the pathology by studying the material from several thousand cases collected during the past 30 years at the New York Eye and Ear Infirmary (where X ray was first used in this country for the detection of intraocular foreign bodies). By selecting those specimens in which the foreign body was present in situ in the histologic section, we have correlated the pathologic with the clinical findings in an effort, where possible, to obtain clues in the treatment of similar cases.

It is difficult to classify the types of reactions which different foreign bodies induce because one particular agent may produce a somewhat different reaction in the same eye depending on the type of tissue involved. Tissues composed principally of fibrous elements will produce a milder reaction than

those containing a considerable amount of epithelial elements. Thus, the reaction in the fibrous tunic or in the optic nerve may be very mild while that in the iris or in the ciliary body is often much more severe. Usually, however, a foreign body which will cause a severe reaction will affect all tissues more strongly than one which will elicit a milder reaction even though there is a different type of response in different tissues. Certain agents, especially those which form chemical compounds with the underlying structures, have an affinity for certain ocular tissues, particularly epithelial elements.

With these facts in mind, in order to evaluate more clearly the clinical aspects of these cases, we have chosen to classify the responses as severe, moderate, and mild, and have compared the early and late reactions. Among the initiators of severe reactions we have selected copper, stone, X-ray radiation, and lime. Examples of the moderate type of reaction are those produced by iron and wood. Cilia and lead are typical agents which will produce mild responses.

SEVERE REACTIONS

COPPER (*chalcosis bulbi*).

Copper (figs. 1A and 1B) often sets up an early severe reaction resulting in the loss of an eye. Some of the copper unites with the underlying tissues to form a chemical compound which is later disseminated throughout the remainder of the eye.

In the uveal tract there is an iridocyclitis and marked leukocytic reaction. In rare instances² only a mild reaction is produced, due to rapid encapsulation of the metal before it has had a chance to combine to any great extent with the tissues.

STONE

Most frequently this agent (fig. 2) initiates a severe inflammatory reaction with

* From the Department of Pathology, New York Eye and Ear Infirmary.

¹ Presented before the Section on Ophthalmology, at the 101st annual session of the American Medical Association, June 10, 1952.

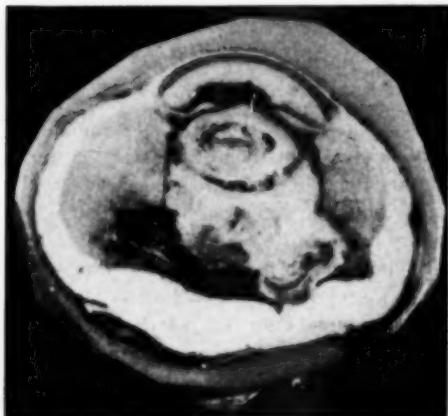


Fig. 1A (Roberts and Schlossman). *Chalcosis bulbi*. Copper in vitreous. Severe inflammatory reaction. Deposition of copper in posterior cortical layers of lens.

abscess formation which ultimately destroys the eye. The chemical composition of stones determines in large measure the severity of the inflammation. Those which contain



Fig. 2 (Roberts and Schlossman). *Stone in vitreous*. Severe inflammatory reaction. Detachment of the retina.

calcium are most soluble and cause the greatest amount of damage.

X-RAY RADIATION (physical)

Radiation may not be considered by some as a foreign body, but because of its ability



Fig. 1B (Roberts and Schlossman). *Chalcosis bulbi*. Copper in vitreous. Diffuse dissemination of copper throughout the globe with greatest deposition in the lens cortex.

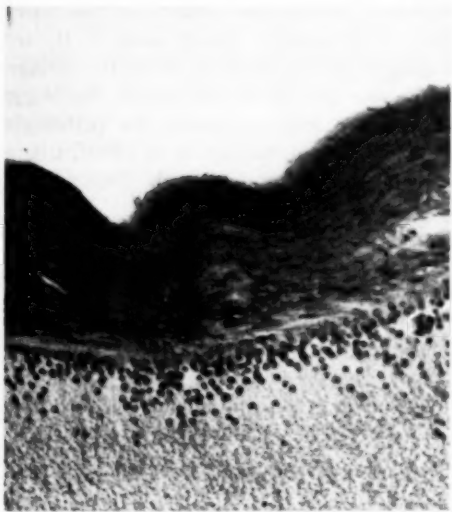


Fig. 3 (Roberts and Schlossman). *Radiation burn*. Early reaction. Loss of epithelium; interstitial keratitis. Absence of fixed corneal corpuscles.

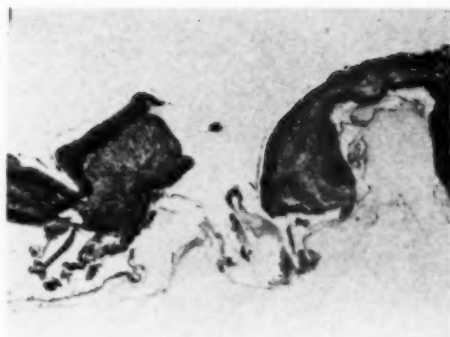


Fig. 4 (Roberts and Schlossman). *Radiation burn. Late reaction. Rupture of cornea.*

to penetrate the globe we have included it in this study. The early reaction is a severe interstitial keratitis which is not particularly characteristic (fig. 3).

Similar to late systemic effects, local damage to the tissue occurring at a later date is much more severe than are the early changes. Thus, quite some time after exposure to radiation, the cornea may rupture (fig. 4) or the characteristic radiation cataract may de-



Fig. 5 (Roberts and Schlossman). *Radiation. Late systemic effect; chronic lymphatic leukemia. Blood vessel in retina longitudinally sectioned, filled with cells typical of chronic lymphatic leukemia.*



Fig. 6 (Roberts and Schlossman). *Lime burn of cornea. Necrosis of corneal stroma with replacement fibrosis and interstitial keratitis.*

velop. Systemically, chronic lymphatic leukemia may develop. Figure 5 exemplifies this condition in the blood vessels of the retina.

LIME (chemical)

This agent produces a severe burn of the cornea. Lime is transformed into calcium hydroxide when it comes in contact with water; this reaction generates a great amount of heat. In addition, the extraction of water

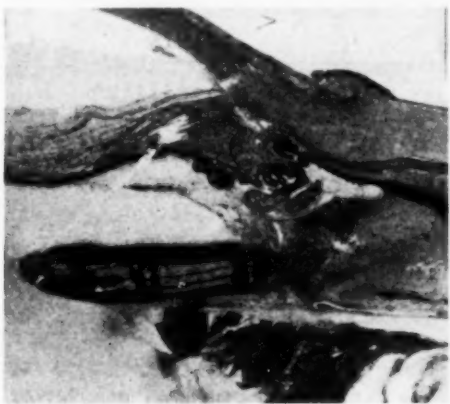


Fig. 7A (Roberts and Schlossman). *Wood in vitreous in close proximity to ciliary body. Early reaction (low power). Marked lymphocytic reaction and hemorrhage.*



Fig. 7B (Roberts and Schlossman). *Wood in vitreous*. Early reaction (high power). Marked lymphocytic response. Presence of small amount of degenerated polymorphonuclear leukocytes. No foreign-body giant cells.

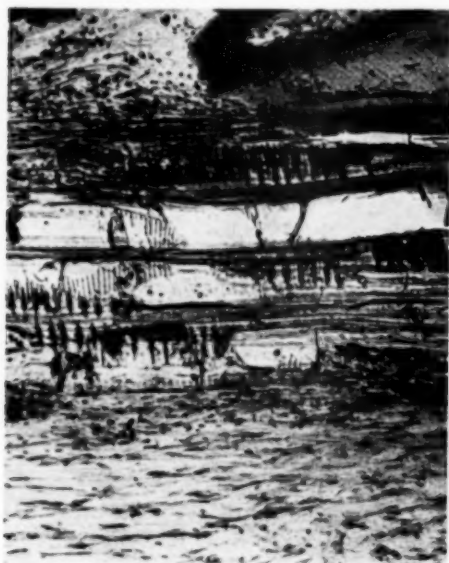


Fig. 8 (Roberts and Schlossman). *Wood in vitreous in close proximity to iris and ciliary body*. Late reaction. Initial inflammatory reaction has subsided and wood is encapsulated by a fibrous tissue mass. A few foreign-body giant cells present.



Fig. 9 (Roberts and Schlossman). *Wood in cornea*. Relatively mild lymphocytic reaction with tendency to encapsulation by fibrous connective tissue. Only occasional giant cells present.

from the tissues leads to necrosis of the cornea. The combination of these two reactions causes the development of interstitial keratitis (fig. 6).

MODERATE REACTIONS

WOOD (vegetable fiber)

In globes removed shortly after the penetration of wood, a moderate amount of pathologic change in the uvea and vitreous was noted, with the lymphocytic response predominating (figs. 7A and 7B).

After several months, a fibroblastic reaction develops and the foreign body becomes encapsulated in connective tissue (fig. 8). In the cornea (fig. 9) and sclera the response to wood is relatively mild, and even shortly after penetration by the foreign body there is very little inflammatory reaction.

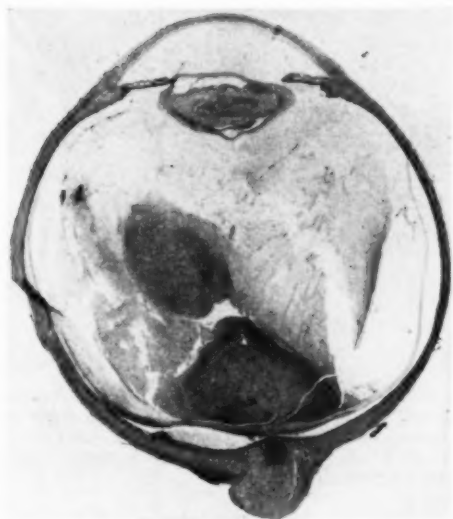


Fig. 10A (Roberts and Schlossman). *Siderosis bulbi*. Iron located in optic nerve. Whole globe.

IRON (siderosis bulbi)

Although there may be cases where it causes a relatively severe reaction, we have classified iron as a moderate irritant. An iron compound is formed at the site of the foreign body and is diffused throughout the tissues, but has a special affinity for the epithelial structures.

It is best studied in the tissues by means of the Perle's sodium prusside stain. The largest concentration of pigment in the eye is at the site of the metal, and this fact is corroborated by the heavy collection of sodium prusside stain in this area (figs. 10A and 10B).

Within a short time after iron has penetrated the eye, siderosis is observed clinically by the characteristic brown ring just beyond the contracted pupil. Soon after the penetration by the metal, proliferation of the lens epithelium is apparent (fig. 11). Later, the irritative phase changes to a destructive one, and the lens epithelium is destroyed (fig. 12).

The nuclear layers are the first to be affected when the retina becomes involved.



Fig. 10B (Roberts and Schlossman). High-power view of Figure 10A. Intense staining of foreign-body bed with sodium prusside stain and diffusion of iron pigment to surrounding area. Inflammatory reaction slight.

Figure 13 shows the presence of iron granules within the phagocytes in the ganglion-cell layer.

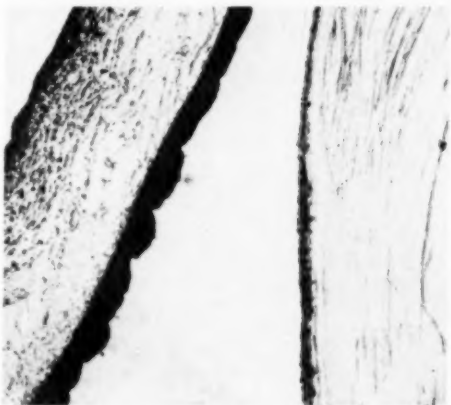


Fig. 11 (Robert and Schlossman). *Siderosis bulbi*. Lens epithelium just beyond pupillary aperture. Early reaction. Iron pigment causes proliferation of the epithelium.



Fig. 12 (Roberts and Schlossman). *Siderosis bulbi*. Lens epithelium just beyond pupillary aperture. Late reaction. Destruction of the epithelium.

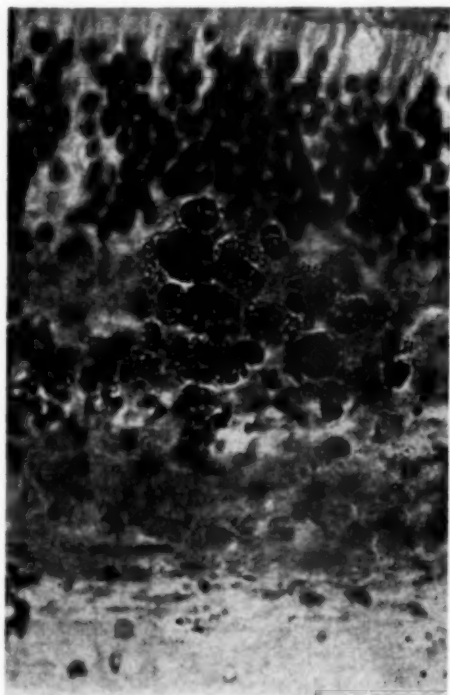


Fig. 13 (Roberts and Schlossman). *Siderosis bulbi*. Posterior retina. Iron pigment granules in large phagocytes in the ganglion cell layer.

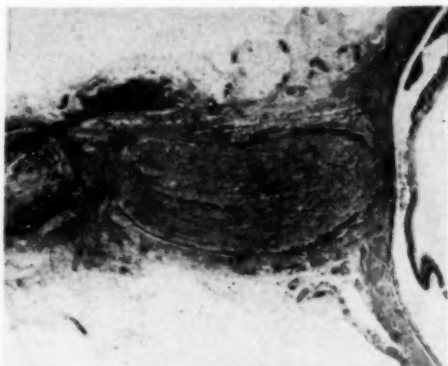


Fig. 14A (Roberts and Schlossman). *Lead in sheath of optic nerve*. Low power. Optic nerve shows laceration. The foreign-body site shows calcification, which is encapsulated in connective tissue. Mild inflammatory response.

MILD REACTIONS

LEAD

This metal, present in most gunshot wounds, initiates a relatively mild reaction no matter where it comes to rest within the eye.

Gunshot is probably nonirritating because the lead becomes covered with a layer of insoluble lead carbonate after it is in contact with the ocular tissue, and does not diffuse.



Fig. 14B (Roberts and Schlossman). High-power view of Figure 14A. Mild inflammatory response at periphery of dense connective tissue. Scattered giant cells.



Fig. 15 (Roberts and Schlossman). *Cilium in surgical wound of cornea*. Encapsulated by fibrous connective tissue. Mild reaction. Several foreign-body giant cells.

Figures 14A and 14B show the mild connective-tissue response within the sheath of the optic nerve.

CILIA

Eyelashes are fairly common foreign bodies which may be carried into the globe by other foreign bodies or during surgery. They are located most frequently in the corneal wound (fig. 15) or in the anterior chamber (fig. 16). At both sites they induce a relatively mild response.

When located in the anterior chamber, they may occasionally become enclosed in cysts. Sitchevska and Payne³ have recently reported this type of case. Except for its pigment which may be absorbed, a cilium will remain essentially unchanged even after long periods of time.

FOREIGN-BODY BEDS

In order to complete this review, it is important to consider the local response at the site of the foreign body. Although the tissues make an attempt to encapsulate the foreign matter, the cellular reaction varies in different parts of the globe. Regardless of the initial cellular response, fibrous connective tissue and foreign-body giant cells of the Langhans type soon invade the area and form the essential elements of the average foreign-body bed (fig. 17).

One of the most unusual types of reaction may occur in the region of the ora serrata or of the optic nerve. It is often referred to as a "Schwiele" (callus) and has a yellowish appearance in the fresh specimen.

The irritation by the foreign body causes proliferation of pigment epithelium and formation of fibrous connective tissue which later becomes hyalinized. Thus, the two essential elements of this pathologic phenomenon are pigment deposition and hyaline tissue (fig. 18).

It is not known why these two areas alone develop this type of reaction; but one may speculate that, since the vitreous body is attached to the retina at these points, the stress due to the pull of the vitreous may be an important factor.



Fig. 16 (Roberts and Schlossman). *Cilium in anterior chamber*. Encapsulated by fine fibrous connective tissue. Mild inflammatory reaction. No giant cells present.

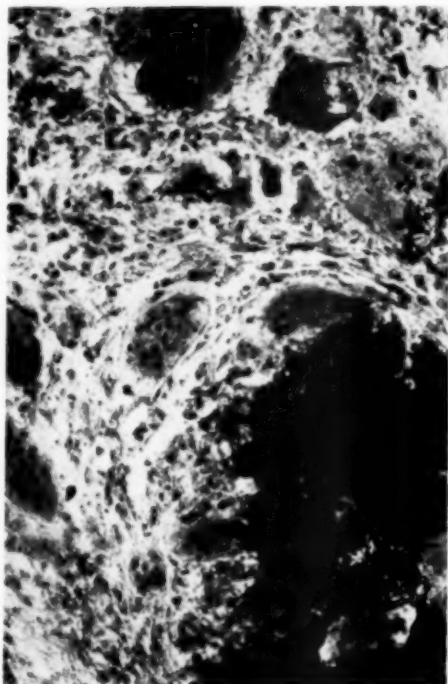


Fig. 17 (Roberts and Schlossman). *Foreign-body bed in sclera due to iron.* Presence of fibrous connective tissue and large giant cells of Langhans type.

A different type of unusual reaction may occur in the anterior chamber. Here the response is similar to that in any serous cavity, and cholesterol crystals are formed in addition to the usual giant cells and connective tissue (fig. 19). The crystal formation is probably due to some reaction in the fat metabolism.

PRACTICAL CONSIDERATIONS

Wherever there is the remotest possibility of the presence of a foreign body in a patient who gives a history of injury, X rays should be taken of the eye and orbit.

From the present study it is obvious that the more severe the reaction produced, the more important it is to remove the foreign body within the shortest period of time. This is especially true of copper and stone, be-

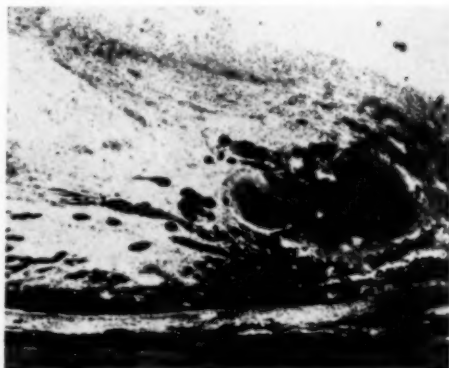


Fig. 18 (Roberts and Schlossman). *Foreign-body bed in region of ora serrata. "Schwiele."* Marked proliferation of pigment epithelium. Presence of hyaline tissue which takes homogeneous eosinophilic stain.

cause their presence will usually cause intractable iridocyclitis and eventual loss of the eye.

It is important to remove iron quickly because this metal may become disseminated throughout the globe and may cause reactions remote from the site of the foreign body. On the other hand, glass, lead, aluminum, and some of the newer alloys cause very

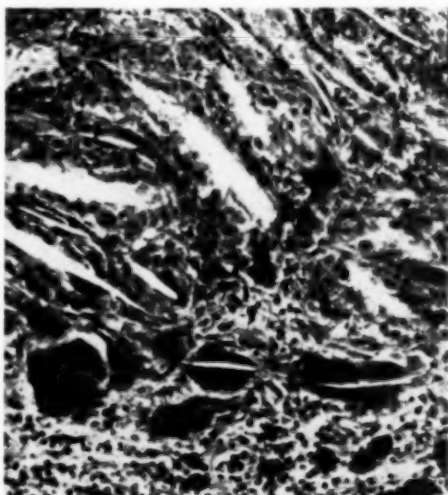


Fig. 19 (Roberts and Schlossman). *Foreign-body bed in anterior chamber.* Presence of cholesterol crystals (cigar-shaped spaces). Fibrous connective tissue and giant cells.

little reaction, and in cases where removal is too difficult the foreign material may be permitted to remain within the globe. We have seen cases in which glass has been tolerated for many years without any untoward effects.

Finally, we would like to advise caution in the use of radiation therapy. The interstitial keratitis in a patient with trachoma shown in Figure 3 was severely aggravated by beta radiation; subsequently it was found necessary to remove his eye due to secondary glaucoma.

SUMMARY

1. Foreign-body reactions may be classified as severe, moderate, and mild.
2. A foreign body may cause a different type of response in different tissues.
3. Examples of severe reactions are those due to copper, stone, X-ray radiation, and lime. Wood and iron cause a moderate type

of response, while cilia and lead are examples of mild irritants.

4. Foreign-body beds are formed by fibrous connective tissue and Langhans giant cells.

5. The "Schwiele" which may occur in the regions of the optic nerve or ora serrata is essentially hyaline tissue and pigment deposition. Cholesterin crystals may be present in the anterior chamber.

6. From the pathologic responses of the eye to various types of foreign matter, the ophthalmologist can obtain a better idea as to those foreign bodies which must be removed immediately, and those which may be allowed to remain if extraction is impossible.

7. If there is the remotest possibility of the presence of a foreign body, X rays of the eye and orbit must be taken.

880 Fifth Avenue (21).

667 Madison Avenue (21).

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DISCUSSION

HELEN C. WILDER (Washington, D.C.): Dr. Roberts and Dr. Schlossman have presented their observations on clinical and pathologic reactions to ocular foreign bodies, particularly copper, stone, wood, iron, lead, and cilia, as well as to lime burns of the cornea and to X-ray radiation. This discussion will be confined to that part of the paper which relates to intraocular foreign bodies.

The importance of their paper lies in its stress on the ability of certain chemical substances to produce mild or violent inflammatory reactions. The point that the chemical composition of stone is responsible, at least in part, for a variation in severity of reaction is well taken.

It must, however, be kept in mind that a similar variation exists in metallic foreign

bodies. Those classified as iron may be only friable flecks of iron rust or they may be solid fragments of stainless steel. So-called lead bullets may contain varying amounts of arsenic, nickel, copper, and tin. Copper usually contains such alloys as nickel, tin, and iron.

It must also be taken into consideration that foreign bodies may carry with them either pathogenic or saprophytic organisms. In a review of 24 eyes in the Registry of Ophthalmic Pathology, with copper particles retained from two days to nine years, there was, in 14, no pathologic evidence that anything more than a low-grade inflammatory reaction had ever existed.

One of the eight in which abscess formation was present contained many colonies of

gram-positive cocci obviously introduced into the vitreous chamber with the missile which had lodged in that location.

In intraocular fragments of dead wood there were often observed saprophytic fungi within vegetable cells and in association with one there were chromoblastomyces which appeared to have multiplied intraocularly, and had incited an acute purulent response. A thorn was responsible for aspergillus infection in the vitreous.

Whenever a purulent reaction is found associated with a foreign body the presence of pathogenic organisms must be ruled out before a reaction to chemical substances can be accepted.

The subject of intraocular foreign bodies is, as the authors have observed, a vital and timely one and their paper has contributed to the knowledge of pathologic response to such particulate matter. However, it is hoped that they will reconsider the value of controlled animal experimentation, with a wider variety of substances than have been utilized in the past for ocular implantations.

It is believed that such experiments with foreign bodies of quantitatively and qualitatively known composition introduced into the eyes of animals under aseptic conditions, when the degree of initial damage as well as the period of retention can be accurately estimated would add immeasurably to their clinicopathologic observations.

DR. H. E. THORPE (Pittsburgh, Pennsylvania): Dr. Wilder pointed out that infection must be considered. I think infection must always be taken for granted in any intraocular foreign body condition. I assume that infection is present unless I can prove otherwise.

From the standpoint of a clinical concept,

one should decide as to the type of copper which has entered the eye. I have observed that yellow copper produces the more serious reaction and is associated with a great deal more exudate and inflammation.

On the other hand, red copper, or charred copper, produces very little immediate inflammatory reaction, and sometimes may remain in an eye for quite a while before there is evidence of serious damage. It may be a year or two before chalcosis takes place.

It is interesting to note that chalcosis is first observed in the region of desquamated membrane under the upper lid, near the upper limbus. The next place where chalcosis will appear is in the cornea near the lower limbus. The lateral and medial limbus that is desquamated in that region is seldom affected, or is affected very late.

It has been said that stainless steel produces very little effect; however, I have seen quite severe ophthalmitis due to stainless steel.

I have observed that siderosis, although present in an eye, may disappear after a number of years following removal of the particle. In cases of very minute particles which could not be removed and which subsequently went into solution (at least they could not be demonstrated by various types of X ray), the siderosis has subsequently cleared.

When cilia, not accompanied by infection, are introduced into the anterior chamber, they generally produce very little trouble unless the root of the cilia is present.

Wood foreign bodies, in my experience, give rather serious trouble. In several cases in which wood splinters have entered the eye, sympathetic ophthalmia has developed later.

TECHNIQUE OF CORNEAL TRANSPLANTATION*

LOUIS DAILY, JR., M.D., AND RAY K. DAILY, M.D.
Houston, Texas

Corneal transplantation was first attempted many years ago, and the history of the operation up to 1948 has been recorded.¹ Surgical techniques for the procedure have been described in English.²⁻⁴

In this paper a technique of corneal transplantation is explained in detail and five cases in which this technique was employed are reported. Marked improvement in visual acuity was obtained with this technique.

TECHNIQUE

Certain procedures were adopted by us from other surgeons and the instruments which we used were designed by others. We combined these procedures and in addition report the routine use of curare and cortisone in corneal transplantation in human eyes.

INSTRUMENTS

Figure 1 shows the instruments employed in uncomplicated partial penetrating keratoplasty.

We have used trephines designed by Franceschetti and Castroviejo. Both are satisfactory. A trephine must be very sharp in order to avoid excessive pressure upon the cornea while trephination is done on the recipient eye.

In one of our cases, herniation of the lens into the hole in the cornea followed trephination with excessive pressure upon the cornea by the trephine. Although final vision of this eye was 20/20 through a spectacle lens which neutralized the refraction error of aphakia, we do not desire repetition of this complication, and now use a sharp trephine which cuts through the cornea without much pressure.

Of equal importance is the use of sharp

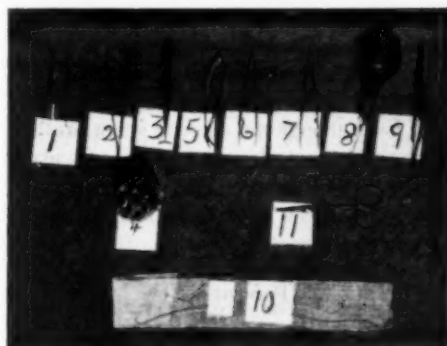


Fig. 1 (Daily and Daily). Instruments for uncomplicated partial penetrating keratoplasty: (1) Speculum. (2) Rectus muscle forceps. (3) Fixation forceps. (4) Corneal trephines. (5) Corneal scissors. (6) Corneal forceps, small teeth (Castroviejo). (7) Corneal forceps, large teeth (Castroviejo). (8) Rubber bulb and cannula. (9) Needleholder. (10) Sutures and needles. (11) Suture scissors.

needles. Needles, designed by Vogt and Barraquer and manufactured by Grieshaber, that are five and seven mm. in length are used. Since the diameter of these needles is smaller than the corneal needles 10 mm. in length, they make smaller holes in the transplant.

The sutures are of 6-0 black silk. Corneal forceps with fine teeth, designed by Castroviejo, hold the graft while sutures are placed.

Fixation forceps are used to steady the recipient eye during trephination. These forceps, designed by Barraquer and Loveras, are applied to the conjunctiva close to the limbus and enable the surgeon to steady the eye without assistance during trephination. Small scissors with blunt tips are used, if necessary, to complete the section. We have used straight corneal scissors designed by Castroviejo.

The needleholder must hold the small needle firmly. We have found the one de-

*Dedicated to Prof. Dr. Karl Lindner, head of the Second Eye Clinic of the University of Vienna, on the occasion of his 70th birthday.

signed by Kalt to be satisfactory.

A physiologic solution of saline is dropped from a medicine dropper or rubber bulb and cannula to wash away pigment from the graft after trephination and to moisten the operative field periodically.

Essential to corneal transplantation are spectacles which will magnify the operative field. Even though the surgeon is not presbyopic, such spectacles enable him to place sutures with accuracy. The surgeon operating in these cases (L. D., Jr.) uses a set of telescopic spectacles.*

PROCEDURE

PREOPERATIVE PREPARATION

Preparation of the patient for corneal transplantation is like that for extraction of cataract, except that pilocarpine is instilled preoperatively into the eye of the recipient in order to contract the pupil. Two drops of a four-percent solution of pilocarpine nitrate are instilled on the night before surgery, one and two hours before surgery, and just before trephination. This is done in order to prevent the partial dilation of the pupil which would otherwise follow ciliary-ganglion blocking.

Preoperative preparation also includes administration of vitamins, restriction of food for several hours before surgery, an enema, and induction of basal analgesia by 0.2 gm. amytal and 0.05 gm. of Demerol† on the night before surgery. If nausea follows the administration of these drugs, they are not used again; 0.2-gm. amytal, 0.1-gm. of Demerol, and 0.0013-gm. of atropine are administered about one hour before surgery. A preparation of penicillin which will maintain a therapeutic level in the blood for 24 hours is injected one day before and on the day of surgery.

* These spectacles are modeled after the surgical telescopic spectacles of Zeiss and are manufactured by Cameron Surgical Specialty Company of Chicago.

† Demerol, sterile aqueous solution of meperidine hydrochloride, Winthrop and Stearns, Inc., New York.

INSPECTION OF EYE OF DONOR

Before any surgical procedure is begun, the eye of the donor is inspected carefully. If there is any doubt as to its suitability, it is rejected and, if another eye is not at hand, the operation is postponed. A donor eye need not look alive to be satisfactory. Only one of the corneas which we used appeared to be as transparent as normal cornea. The other corneas exhibited loss of transparency of various degrees, but never to such degree as to obstruct the view of the pupil.

ANESTHESIA AND AKINESIA

After the operative field is cleansed, akinesia is obtained by injection of a solution of procaine and hyaluronidase‡ into the peri-orbital region of the face. This solution is also injected into the outer canthus and into the lids.

Anesthesia of the eye is begun with instillation into the conjunctival sac of drops of a solution of 0.5-percent pontocaine. Instillation is begun about 10 minutes before trephination and is repeated at intervals of two minutes for four times. Epinephrine§ is also instilled.

No longer than five minutes before trephination of the recipient eye, a retrobulbar injection is made with a long needle of small diameter. The solution which is injected contains 1.0 mm. of 2.0-percent procaine to which has been added six turbidity units of hyaluronidase, one drop of epinephrine, and four drops of 80-percent ethyl alcohol.

The operative field is surrounded by sterile sheets. Instruments are placed within reach, and a needle is introduced by an assistant into a vein at a distance from the sterile field.

After the lids have been retracted by the speculum, a suture is passed beneath the superior rectus muscle but is not made taut.

‡ Wydase-lophilized hyaluronidase, Wyeth, Inc., Philadelphia.

§ Adrenalin (1:1,000) Parke Davis and Company, Detroit.

This suture is left in position until the completion of surgery. Traction upon it is indicated only when movements of the eye interfere with placement of sutures.

About four minutes before trephination, 0.3 ml. of curare* is injected by an assistant through the needle which was introduced into a vein at a distance from the sterile field. An injection of this quantity is repeated at intervals of one minute until a sufficient amount of curare has been given. More curare may be injected if needed later in the operation.

All the precautions listed by Cordes⁵ should be observed in administration of curare. Trephination is usually completed before injection of curare is ended since the total dose of curare is seldom more than two to three ml.

In trephination, the trephine must be centered accurately. This is not always easy to do on conical or clouded corneas but it must be done carefully. The trephine is centered by observing the eye of the patient with one eye only. Gaze is directed straight at the patient's eye and the trephine is placed so that it is equidistant from the corneal limbus in all directions.

Trephination of the recipient eye is performed carefully and rapidly with as little pressure as possible. The trephine is withdrawn quickly as soon as aqueous escapes from the anterior chamber, and section is completed carefully with scissors. After completion of section and removal of the corneal disc, loose tags of Descemet's membrane are grasped with forceps and excised. Then the corneal disc is replaced in the hole from which it had been removed and is left there until the graft is prepared.

The donor eye, inspected just before surgery to determine its suitability, is now trephined with the same trephine used on the recipient. The entire thickness of the donor cornea may be cut since injury to the under-

lying structures is of no consequence.

The donor eye, wrapped with gauze, is held in one hand with enough pressure to make it as firm as a living eye, while trephination is done with the other hand.

After trephination, the graft is left in place while one suture is placed in its margin at a depth of less than one half of the thickness of the cornea. Suspended by this suture, the transplant is inspected. If pigment is observed, it is washed away with physiologic saline. The transplant is then transferred to the eye of the recipient and is carefully sutured to the recipient cornea.

The suture which is in the transplant is placed in the cornea of the recipient and tied. Another suture is placed on the opposite side of the transplant and tied. Additional sutures are placed until the wound is closed by sutures which are placed one mm. apart. Usually there are 10 (when the diameter of the transplant is six mm.).

After all of the sutures are in position, the cornea is covered with a piece of membrane from the inside of the shell of a recently boiled egg. A suspension of 2.5-percent cortisone[†] is dropped on the eye. An ointment of 0.25-percent eserine is introduced into the conjunctival sac, as well as an ophthalmic ointment of aureomycin. The lids are closed and a binocular bandage is applied. A metal shield is placed over the bandage of the operated eye.

The patient is lifted onto a stretcher and from the stretcher into bed.

POSTOPERATIVE CARE

CHANGE OF BANDAGE AND TOPICAL MEDICATION

The bandage is changed every two days after the third postoperative day. At each change, an ointment of cortisone is instilled into the conjunctival sac as are atropine and aureomycin ophthalmic ointment. The op-

* Mecostin Chloride, dimethyl-tubocurarine chloride, 1 mg. per cc. equivalent to 20 units as Intocostin, E. R. Squibb and Sons, New York.

† Cortone (cortisone acetate 2.5 percent, ophthalmic) Merck & Company, Inc., Rahway, New Jersey.

posite eye is uncovered on the fifth post-operative day.

Sometimes the egg membrane is found to be extruded part way through the palpebral fissure at the first change of bandage. If not, curiosity usually impels the surgeon to remove it with forceps in order to inspect the eye. After removal of the membrane, photophobia and blepharospasm increase sharply so that, when the bandage is changed, a solution of 0.5-percent pontocaine should be instilled before the eye is inspected.

ACTIVITY OF PATIENT

Patients may use a bedside commode on the second day after surgery and may sit in a chair after from three to seven days.

Enemas and laxatives are given as indicated after the first postoperative day and the patient is cautioned not to strain at stool.

Patients should be cautioned not to bend, stoop, or lift and to avoid any form of exertion.

SYSTEMIC PENICILLIN

Penicillin is administered systemically for several days after surgery.

DIET

Liquids are given through a straw on the day of surgery. Afterward, a general diet, with ground meat, which does not require the patient to chew too heavily is permissible. This diet is supplemented with vitamins.

REMOVAL OF SUTURES

Sutures are removed on the 12th day after surgery. This is done while the patient is lying on a table, after akinesia and repeated instillations of a solution of 0.5-percent pontocaine.

A speculum holds the lids away from the globe, and sutures are removed carefully with a sharp Graefe knife or razor blade and forceps. While sutures are removed, the surgeon uses telescopic spectacles to provide magnification. If the anterior chamber is lost while a suture is being removed, removal of

all sutures is completed and a solution of pilocarpine and ointment of cortisone are instilled.

REMOVAL OF BANDAGE

The eye must be bandaged until no ectasia of the transplant will occur after removal of the bandage. It is safe to remove the bandage from the operated eye 20 days after transplantation of a graft which is six mm. in diameter.⁴

After removal of bandage, ointment of cortisone is instilled every two hours while the patient is awake. Frequency of instillation of cortisone may be increased before this time if vascularization of the host cornea or edema of the transplant appears to be excessive.

After the cornea is clear, the eye is refracted and the corneal curvature is measured with the ophthalmometer. These examinations are repeated at intervals of one week. If the corneal curvature increases as indicated by increase of myopic astigmatism, the eye must be bandaged with pressure as described by Castroviejo.³ Cases 4 and 5 are examples of the necessity of bandage with pressure. They will be described later.

When signs of keratitis and uveitis have disappeared, instillations are reduced gradually. The eye should then be observed daily. If signs of uveitis or corneal edema reappear, frequency of cortisone is increased.

Some details of operative technique and postoperative care are illustrated by these case reports.

REPORT OF CASES

CASE 1

This white youth, aged 18 years, had keratoconus. Visual acuity of the unoperated left eye with a contact lens was 20/90. Pre-operative acuity of the right eye was 20/400 with a contact lens, and the apex of the cornea exhibited dense white opacification (fig. 2). A six-mm. graft was secured with 10 sutures after irrigation with Ringer's solution to remove the pigment from the

transplant. Before completion of suture, the transplant was opaque and gray in color.

The eyes were bandaged for three weeks postoperatively. Sutures were not removed, and cortisone was not used until after this time. After removal of sutures, very small blood vessels were seen through the corneal microscope, extending from the limbus of the cornea almost to the border of the transplant. Edema of the stroma of the transplant and folds in Descemet's membrane were also seen.

At this time an ointment of cortisone was instilled into the conjunctival sac; this was repeated regularly for many weeks. Blood vessels disappeared from the host cornea and edema subsided in the transplant while cortisone was used. When edema had gone, a white membranous opacity was seen to cover the posterior surface of the transplant except for a small area in the superior temporal quadrant.

In addition to the development of a membrane on the back of the transplant in this case, another complication, in the iris, is of interest. Three weeks after surgery, a small yellow nodule was seen with the corneal microscope in the iris at the 4-o'clock position. Delicate bands of tissue extended from this nodule in all directions. The margin of the pupil was displaced toward the nodule and the shape of the pupil resembled that of a pear. While cortisone was administered



Fig. 3 (Daily and Daily). Postoperative appearance of eye shown in Figure 2. Note corectopia which developed after corneal transplantation.

topically, this nodule disappeared, but the corectopia (fig. 3) has persisted.

After corneal transplantation, visual acuity of this right eye with a +2.0D. sph. \ominus -7.0D. cyl. ax. 36° was 20/60; with a contact lens, visual acuity was 20/30. Nineteen months after surgery, a contact lens which retains fluid between cornea and lens cannot be worn for one hour without corneal edema reducing visual acuity in this eye.

Some difficulty has been experienced in selecting a corneal contact lens which will stay in proper position before the cornea, but corneal edema has not followed the use of a corneal lens for a period of four hours. All corneal contact lenses which have been worn have been in firm contact with some of the surface of the transplant.

Discussion. The postoperative course of Case I, when compared with our other cases, suggests that neither were sutures removed nor was cortisone administered soon enough after corneal transplantation. Multiple corneal sutures appeared to stimulate vascularization of the host cornea and to foster uveitis. Cortisone apparently inhibited the vascularization.

Review of the ophthalmic literature has not disclosed mention of a nodule in the iris producing corectopia. We believe that the iris nodule in our case, which appeared to be surrounded by bands of stromal tissue under tension and which produced corectopia, was a small granuloma. This lesion, we believe, was part of the anterior uveitis which followed corneal transplantation. A

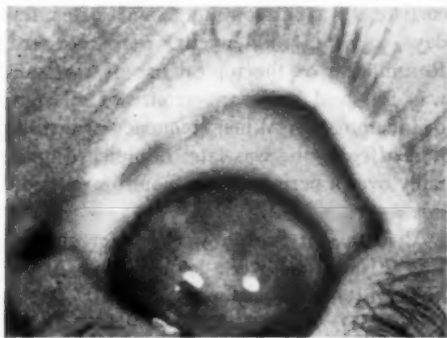


Fig. 2 (Daily and Daily). Preoperative appearance of eye with keratoconus.



Fig. 4 (Daily and Daily). Postoperative appearance of eye with keratoconus, front view.

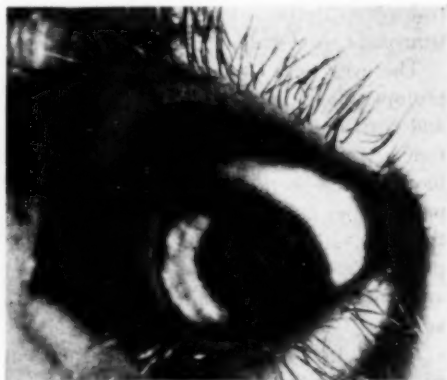


Fig. 5 (Daily and Daily). Postoperative appearance of eye with keratoconus, side view.

similar nodule observed in one iris of a 49-year-old man who had no other evidence of uveitis, produced marked corectopia and anterior peripheral synechias and may have represented the initial stage of essential atrophy of the iris.

We believe that, in Case 1, cortisone helped to arrest opacification of the back of the transplant, to clear the stroma of the transplant of edema, to control uveitis, and to resolve the iris granuloma.

CASE 2

This woman, aged 48 years, has advanced corneal dystrophy of the type first described by Groenouw. Visual acuity of each eye before surgery was recognition of hand movements at a distance of one foot. Surgery was complicated by loss of the lens after trephination. In spite of this complication, after discission of a secondary cataract, visual acuity of 20/20 was obtained with a spectacle lens of +11.5D. sph. \ominus +2.0D. cyl. ax. 70°. This case is reported in detail elsewhere.⁶

Discussion. We concluded from Case 2 that, while loss of lens in keratoplasty is a serious complication, it need not result in permanent serious damage to the eye or loss of vision. After this complication we began to use curare routinely, and also took pains in the selection of sharp trephines.

CASE 3

This girl, aged 16 years, has keratoconus with preoperative visual acuity with contact lenses of: R.E., 20/40; L.E., 20/50.

Corneal transplantation was done on the left eye and a six-mm. graft was secured with 11 sutures. Ointment of cortisone was instilled once daily between the first and fourth postoperative weeks. At this time vascularization of the host cornea extended almost to the inferior border of the transplant. Frequency of instillation of cortisone was increased to every two hours, and vascularization of the host cornea disappeared slowly while cortisone was used; the transplant also became very transparent.

Seven weeks after surgery, instillation of cortisone was discontinued and, after five days, signs of mild uveitis were observed. Resumption of the topical use of cortisone was followed by disappearance of all signs of inflammation. When frequency of instillation of cortisone was later diminished gradually over a period of one month, uveitis did not return.

Visual acuity seven weeks after surgery was 20/50; one week later it was 20/40; and eight months postoperatively, 20/30 with a -0.25D. sph. \ominus -2.75D. cyl. ax. 135° (figs. 4 and 5).

Discussion. In this case, postoperative uveitis was controlled by cortisone ointment. Before surgery, the patient could read through a contact lens. After corneal transplantation, the patient was able to read through a spectacle lens of relatively low power.

CASE 4

This woman, aged 29 years, has keratoconus. Visual acuity with contact lenses before surgery was: R.E., 20/60; L.E., 20/50. A seven-mm. transplant was secured to the cornea of the right eye with 11 sutures. At surgery, the anterior chamber was absent after trephination and the diameter of the pupil was that of the corneal hole in spite of frequent instillations of pilocarpine. After surgery, the transplant was fairly clear until removal of sutures.

On the 11th postoperative day, after retrobulbar injection of procaine prior to removal of sutures, it was observed that the anterior chamber was absent and that the posterior surface of the transplant was white and exhibited striations. Sutures were removed, a solution of pilocarpine and ointment of eserine were instilled, and a little pressure with a bandage was exerted on the eye. On the following day, the anterior chamber was present and the transplant was grossly transparent again.

Seventeen days after surgery the corneal microscope showed that the transplant was clouded and that no vessels were present in the cornea. It was also observed that the nasal edge of the transplant was flattened. At this time, instillation of cortisone ointment was increased to every two hours while the patient was awake.

Eleven days later only folds in Descemet's membrane were observed and seven days later, about six weeks after surgery, the transplant was completely transparent, and there was no evidence of uveitis.

At this time with a +1.0D. sph. \ominus +4.5D. cyl. ax. 78°, visual acuity was 20/40. Two

weeks later, marked myopic astigmatism was measured with a keratometer and visual acuity with a -14.5D. cyl. ax. 105° was 20/60. About 10 weeks after surgery, myopic astigmatism had increased and with a -23.0D. cyl. ax. 7°, visual acuity was 20/40. At this time the eye was bandaged with pressure as described by Castroviejo,³ and pressure was maintained for one month.

One week after the first pressure bandage was applied, astigmatism was diminished and with a -3.0D. sph. \ominus -7.5D. cyl. ax. 15°, visual acuity was 20/50. After removal of the last pressure bandage, visual acuity with a -4.0D. sph. \ominus -5.75D. cyl. ax. 32°, vision was 20/40.

At no time, however, could the patient read at 15 inches with any spectacle lens. Eight months after surgery visual acuity through a contact lens is 20/30, and she can read.

Discussion. Only in this case was a seven-mm. transplant used, and in this case the transplant progressively increased in curvature. Increase in curvature of the transplant was diminished by bandage with pressure on the eye for one month.

CASE 5

This Negro, aged 16 years, had a vascularized corneal leukoma. When first seen by us in March, 1951, he stated that his right eye had had repeated attacks of redness and pain for many years, and examination disclosed a large ulcer in the center of a cornea which was already scarred.

While under treatment, vascularization increased and, at the end of two months, a sheaf of large vessels coursed from the limbus and ramified in a scar in the center of the cornea. After one year, the eye showed no evidence of inflammation and the vascularized scar reduced visual acuity to 20/400. At this time, corneal transplantation was done and a six-mm. graft was sutured to the cornea of the host with nine sutures.

At surgery an attempt was made before

trephination to obliterate the corneal vessels by application of a heated muscle hook to the nasal edge of the limbus. After trephination, blood issued from these vessels. This proved to us that cauterization had not obliterated these vessels.

Immediately after surgery a 2.5-percent solution of cortisone was dropped onto the eye and this was repeated once daily for seven days. At this time, examination with the corneal microscope revealed some striated keratitis and invasion of vessels into the very edge of the transplant at the 3-o'clock position. At this time, sutures were removed and an ointment of cortisone was applied to the eye. Application was repeated every two hours while the patient was awake.

Five days later, with a +3.5D. sph. \ominus -10.5D. cyl. ax. 120°, vision was 20/60. At this time a bandage was applied with pressure on the eye. After one week, with a +1.75D. sph. \ominus -2.25D. cyl. ax. 100°, visual acuity was 20/50, and bandage of the eye was discontinued.

Ten weeks postoperatively, visual acuity without correction was 20/30, and the patient had normal binocular vision. No evidence of vascularization of the transplant was evident six months after surgery, although vessels extend from the limbus to the opaque scar about the transplant. Cortisone has not been used for four months.

Discussion. In this case, although vascularization of the cornea was present before transplantation, no invasion of the transplant by vessels occurred. In the past, vascularization of the cornea has held an unfavorable prognosis because the corneal vessels invaded the transplant.⁷ We believe that cortisone and multiple simple sutures were important factors in the prevention of vascularization of the transplant in this case.

DISCUSSION

Statistics on the results of corneal transplantation, recently compiled under the auspices of the American Academy of Ophthalmology and based on results of a large

number of operations which had been performed up to 1948 at a number of American hospitals,⁸ showed that results of the operation varied with the disease of the cornea which reduced vision. Even in keratoconus, which was shown to be the disease most favorable for cornea transplantation, successful operations numbered only 65.2 percent and the authors concluded that corneal transplantation should not be done in any eye with a visual acuity better than 20/200.

The validity of the data of this statistical study was questioned by Stansbury⁹ who pointed out that clarity of the transplant and not visual acuity was the criterion of success of the operation in this analysis. He stated that many eyes with transparent transplants do not obtain improved vision, and that such operations are not really successful. Analyzing all cases of corneal transplantation at the Columbia-Presbyterian Hospital in New York, Stansbury⁹ (1950) concluded that, in 13 percent, vision was improved but that, in 35 percent, vision was made worse by the operation, and that, in many cases, the operation resulted in total blindness.

These statistics, which indicate that the results of corneal transplantation are not good, are based on results of operations which differed in technique from the one we describe herein. The most important difference in the techniques is in the method of suture. Very close apposition of the entire circumference of the transplant to the cornea of the host is obtained with multiple, interrupted, simple sutures.

This apposition of transplant to host is of great importance in the prevention of complications,⁴ such as delayed reformation of the anterior chamber, anterior synechias, and glaucoma, which threaten destruction of the entire eye. These complications were not encountered when we used the technique herein described.

Topical application of cortisone is another point of difference between our technique and those techniques described previously. Cortisone may prevent, or reduce in severity,

postoperative edema of the transplant, which French surgeons have called "the malady of the graft," because they encountered it with frequency.¹³

This edema occurs between the third and sixth weeks after surgery and its cause is unknown. It may be an allergic reaction of the transplant to the host, and experimental studies seem to indicate that cortisone may prevent or reduce such edema.¹⁴

We believe that this complication occurred in our fourth case. In this case, the edema disappeared in one week after increasing the frequency of cortisone applications.

Multiple, simple sutures, when combined with topical application of cortisone, may make the prognosis more favorable in certain types of corneal opacities which, in the past, have been considered unfavorable for corneal transplantation.¹⁰ Vascularized leukoma is an example of this type of opacity. It was replaced by a corneal transplant in our fifth case.

Endothelial dystrophy is another type of corneal opacity, which has been considered unfavorable for corneal transplantation.^{10, 11} Recently a case has been reported of successful corneal transplantation in endothelial dystrophy,¹² in which multiple simple sutures were placed with Grieshaber needles between the edge of the transplant and the cornea of donor.

Another type of corneal opacity considered unfavorable for corneal transplantation is one in which the opacity is so large that, after transplantation, no normal corneal tissue borders on the graft.¹⁰ Our second case was one of advanced nodular corneal dystrophy in which the opacities were very dense, occupied all levels of the stroma, and extended to the corneal limbus. Corneal transplantation was successful in this case.

Other additions to our technique which also minimize complications include the use of curare and miotics. Curare tends to prevent extrusion of the lens, as occurred in our second case. Miotics also tend to prevent this complication, and to protect the

lens against injury by the trephine.

In our cases no synechias have followed the use of miotics. The pupillary margin of the iris tends to form anterior synechias at corneal wounds, and in corneal transplantation. At surgery it is easier to keep the pupillary margin of the iris away from the wound by miosis than by mydriasis.

One other factor, which may have contributed to the success of our corneal transplantations, is the use of donor eyes which had been enucleated more than 24 hours before use. All of the eyes which we obtained from the Eye-Bank for Sight Restoration, Inc., were flown from New York City without charge by Eastern Airlines. They were delivered during the night or early morning to our home.

On receipt of the eyes, the ice, which had partly melted, was replaced in the thermos jug. Surgery was performed on the day of receipt of the eyes. All of these eyes have provided grafts which are transparent and have greatly improved the patient's vision. Barraquer stated that the most suitable corneal transplants are from eyes which have been enucleated from 12 to 36 hours before transplantation and have been kept in moist air at a temperature of 2°C. to 4°C.⁴

SUMMARY

A technique of partial penetrating keratoplasty is described and five cases reported in detail illustrate details of operative technique and postoperative care.

This technique includes maintenance of miosis, intravenous administration of curare, multiple simple sutures between the edge of the transplant and host, the application of egg membrane over the cornea after completion of suturing, and the topical application of cortisone to the eye at surgery and postoperatively.

In a case of corneal dystrophy, visual acuity was improved from perception of hand movements to 20/20 by corneal transplantation. In a case of keratoconus, acuity was improved from 20/400 with a contact

lens to 20/40 with a spectacle lens. In a second case of keratoconus, visual acuity was improved from 20/60 with a contact lens to 20/40 with a spectacle lens. In a case of corneal scar, acuity was improved from 20/400 to 20/30 without a corrective lens.

CONCLUSIONS

Improvement in visual acuity, after cor-

neal transplantation by the technique which we describe, indicates to us that the percentage of successful corneal transplantations is increased greatly when this technique is used, and that visual acuity of better than 20/200 is not a contraindication to corneal transplantation.

1117 Medical Arts Building (2).

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OPHTHALMIC MINIATURE

Treatment for Night Blindness

Bleeding at the forearm, purgation of the belly and clysters. The head must be cleared by gargling and sneezing and the veins at the inner corners of the eye must be bled, and he must drink before a meal, water with dry hyssop and rue.

The eye must be anointed with alum, rock salt and the juice that flows from a goat's liver when it is roasted and he must admit to the eyes the steam arising from it during the roasting and then eat the liver.

Hunain Ibn Is.-Haq. (809-877)

The Book of the Ten Treatises on the Eye.

A NEW SURGICAL APPROACH TO MYOPIA*

TUTOMU SATO, M.D., KOICHIRO AKIYAMA, M.D., AND HIROHIKO SHIBATA, M.D.

Tokyo, Japan

I. INTRODUCTION

The problem of decreasing the total refraction of the myopic eye may be approached in three ways:

First, the length of the physiologic axis of the globe may be altered, but this is not practiced at present and is not likely to be in the future.

Secondly, Fukala's method of lens extirpation is already in use, but indications for this procedure do not apply even to one half of one percent of all cases of myopia.

Thirdly, there seems no alternative method other than changing the refractive power of the cornea, and the present communication reports the results of 32 cases of myopia treated by appropriate anterior and posterior corneal incisions. This new concept was developed from our clinical studies¹⁻⁵, and from experimental research on animals^{6,8} as well. It is designed to reduce the refractive power of the eye.

It was found that scars produced by anterior (or surface) and posterior incisions in the extrapupillary areas of the cornea resulted in a lengthening of the radius of the corneal curvature overlying the pupil, thereby decreasing its refractive power. The present method was attempted on the human eye after sufficient encouragement had been obtained from experimental studies on the rabbit eye.⁶

Scarification of the anterior corneal layers in the extrapupillary zone produced, in the rabbit eye, weak and impractical changes in the refractivity of the cornea. Since similarly accomplished incisions into the posterior corneal layers produced a maximum hypermetropic effect of two diopters, it seemed possible, therefore, to utilize this method in cases of mild myopia. (These

clinical experiences have been summarized by Akiyama in the *Acta Soc. Ophth. Japonicae*, 56:1142, 1952).

If clinically practical results are to be expected in cases of advanced myopia, it would appear that incisions of both the anterior and posterior corneal surfaces offer the most logical probability, and we submit "anterior and posterior half-corneal incisions" as the most suitable description of our procedure.

II. TECHNIQUE

Before surgery, refraction is carefully determined both objectively and subjectively. The axis and degree of astigmatism, if it is present, is carefully determined, for the operation may be aimed not only at reducing the total myopia but also at the development of a neutralizing hypermetropic corneal astigmatism at the opposite axis.

Suitable miosis induced prior to operation is useful in determining the exact pupillary area of the cornea. After adequate topical anesthesia, the cul-de-sac is irrigated liberally with a mild antiseptic, and a retrobulbar injection of three cc. of novocaine is given. This not only restricts motility of the globe, but actually creates a slight exophthalmos

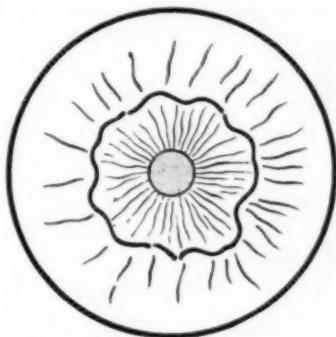


Fig. 1 (Sato, Akiyama, and Shibata). Satisfactory miosis is accomplished.

* From the Juntendo Medical College.

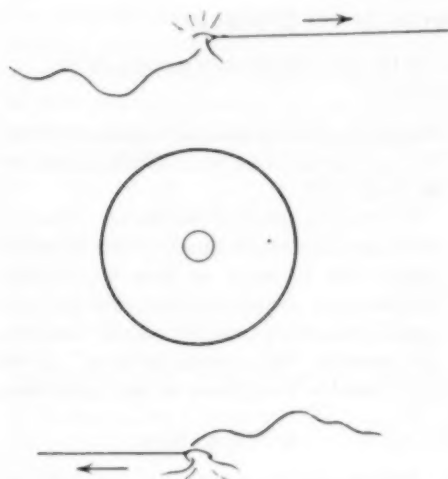


Fig. 2 (Sato, Akiyama, and Shibata). Two bridle sutures are placed under the tendons of the superior and inferior rectus.

which facilitates the maneuvers of the operation.

Bridle sutures are placed under the tendons of the superior and inferior rectus muscles, these permitting rotation of the globe about its antero-posterior axis (fig. 2). They are used at the time the corneal knife is introduced into the anterior chamber from above or below (figs. 5 and 6).

A small and simple lid retractor, such as the Knapp type, is inserted between the lids, and a sterile gray hair or a fine, white fish gut is placed on the cornea to afford adequate visualization of the pupillary zone (fig. 4).

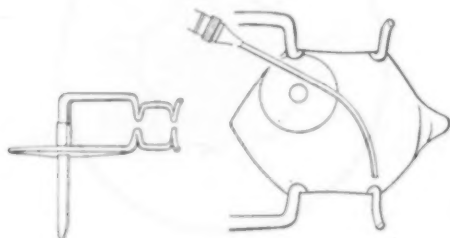


Fig. 3 (Sato, Akiyama, and Shibata). Retrobulbar injection. At the left is a Komoto retractor.

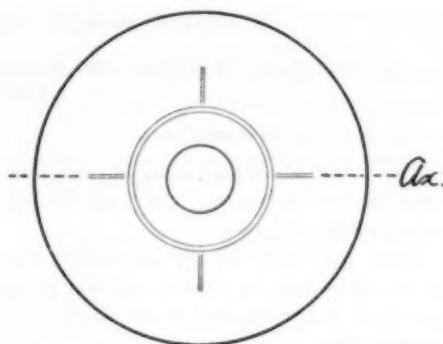


Fig. 4 (Sato, Akiyama and Shibata). Five gray human hairs are used as guides for the incisions. To make a loop, twist the hair in the manner of a wire hoop. If astigmatism is combined with myopia, four pieces of straight hair are laid on the main meridians. (In the following pictures the hair is not illustrated.)

Sato's corneal knife is inserted into the anterior chamber from the superior limbus and five to nine posterior half-incisions are made in the lower portion of the cornea (fig. 5). The knife is now withdrawn and immediately reinserted into the chamber from the inferior limbus and similar incisions, five to nine in number, are made into the upper portion of the cornea. Similarly, temporal

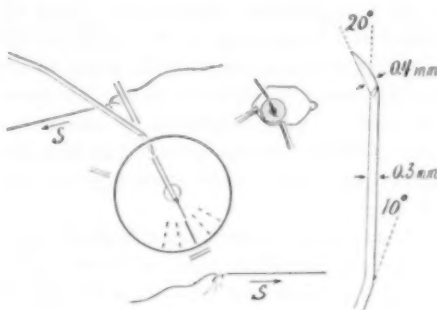


Fig. 5 (Sato, Akiyama, and Shibata). Illustrating the technique of inserting the knife into the anterior chamber, superiorly. After the knife is inserted, posterior incisions are made in the lower quadrant of the cornea. — This mark shows the position of the fixation forceps. Attention is directed to the position of the globe and the proper use of bridle sutures. The corneal knife must conform exactly to the design of the Sato corneal knife. The length of the blade is 2.5 mm.

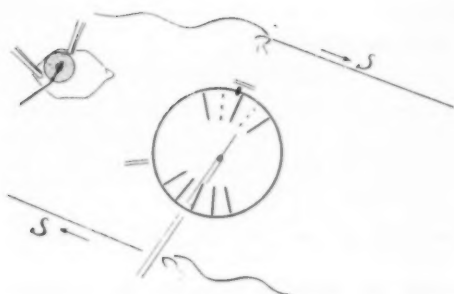


Fig. 6 (Sato, Akiyama, and Shibata). Superior quadrant incisions. Note the use of bridle sutures.

incisions are made from the nasal side (fig. 6) and, finally, nasal incisions are performed from the temporal side (fig. 7).

The knife is introduced through the corneoscleral transition zone, slightly to the scleral side, and reaches the anterior chamber after approximately two mm. of tangential tunnelling through the corneal stroma.

With due regard for iris and lens, the knife is carried across the anterior chamber to the opposite limbal zone, and an incision of sufficient length to allow for a pupil of approximately six-mm. diameter is made.

The posterior incisions are made clear through the endothelium, Descemet's membrane, and approximately two thirds of the corneal stroma; adequate length without sacrifice of the pupillary zone, as well as uniform depth, are emphasized.

There is a natural tendency for the starting and terminal points of the wound to become more shallow than the middle, but this should be avoided since the short, shallow "boat-bottomed" incisions are less effective.

The depth must be kept even and sufficient throughout the entire extent of the incision.

When the incision has reached its termination, the point of the corneal knife must be definitely separated from the posterior surface of the cornea. Assurance that disengagement of the knife tip has been accomplished is obtained by slight to-and-fro movements of the blade before it is carried

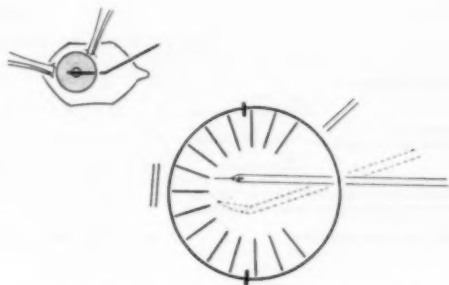


Fig. 7 (Sato, Akiyama, and Shibata). Completion of incisions in the lateral quadrant. In withdrawing the knife from the anterior chamber, disengage the point of the knife from the cornea in the manner illustrated by the dotted line. This maneuver is made in order to avoid harm to the pupillary zone.

again to the limbal zone prior to the next incision.

This precaution is also very important just prior to the withdrawal of the knife from the anterior chamber.

If, by chance, the posterior half-incision perforates the cornea in some small sections of the wound, there is almost no cause for worry except possibly that the decreased depth of the chamber may hinder the operation. If the chamber depth does become annoyingly shallow during the operation, a waiting period of 15 to 30 minutes will usually allow for restoration of almost normal depth.

Aqueous seepage from the self-sealing puncture is rare, if it occurs at all; however, application of a spatula tip for a few seconds will stop it promptly.

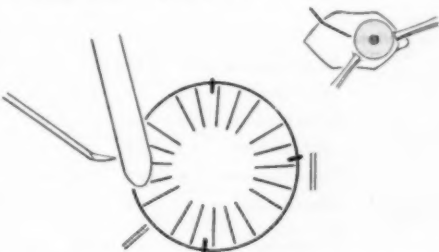


Fig. 8 (Sato, Akiyama, and Shibata). Completion of nasal incisions. After each withdrawal of the knife from the anterior chamber, press the wound lightly with a spatula to avoid leakage of aqueous.

TABLE 1
EFFECT OF THE TREATMENT MEASURED OBJECTIVELY

Case Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Refraction (myopia in diopters)	Before Operation	2.5	15.0	8.5	11.0	3.0	8.0	8.5	7.0	3.5	12.0	5.0	3.5	2.0	10.0
	After Operation	2.0	13.0	7.0	9.0	1.5	3.0	7.0	2.5	0.5	7.0	3.0	1.0	1.0	6.0
	Reduction	0.5	2.0	1.5	2.0	1.5	5.0	1.5	4.5	3.0	5.0	2.0	2.5	1.0	4.0
Reduction in main meridian in high-degree astigmatism (increased astigmatism)			4.0	2.5	4.0		5.0	2.0	3.5 (1.0)	2.5	4.0 (1.0)				8.0
No. days after operation		30	42	45	17	124	44	22	36	31	21	61	42	70	27

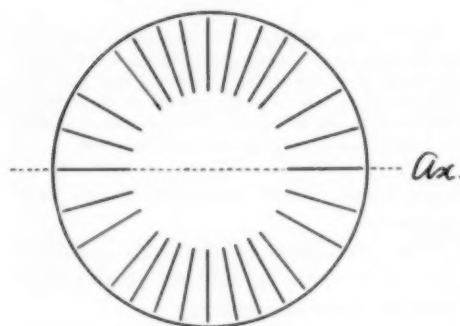


Fig. 9 (Sato, Akiyama, and Shibata). The picture illustrates the completion of the posterior half-corneal incisions of which as many as 36 can be made. If myopic astigmatism is present, the incisions in the quadrants containing the meridian of highest degree should be deeper, longer, and greater in number than those in the quadrants with a lesser degree of myopia.

The procedure is facilitated by a sharp knife, and, because of the delicacy of the instrument, two knives must always be selected prior to operating since one may be-

come too blunt to complete the surgery. The knife blade is 0.4 mm. wide, being a very slight expansion of the blade shaft, 0.3 mm. in diameter. At a point 12 mm. from the tip of the blade, the shaft is bent 10 degrees as shown in Figure 9.

Radial incisions of the anterior surface of the cornea are accomplished with Okamura's trachoma knife, the construction of which does not permit incisions deeper than the operator intends. This instrument is similar in construction to the Lancaster sclerotome of American manufacture. About 40 incisions are made from the peripupillary zone of the cornea to the limbal sclera and deep enough just to avoid perforation. After completion, the corneal incisions have an appearance similar to the bamboo frame of a Japanese umbrella.

III. POSTOPERATIVE TREATMENT

After surgery, the eye is atropinized and penicillin instilled into the conjunctival sac.

TABLE 2
EFFECT OF THE TREATMENT MEASURED SUBJECTIVELY

Case Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Unaided Vision	Before Operation	0.3	0.02	0.09	0.02	0.2	0.1	0.2	0.1	0.1	0.01	0.1	0.1	0.3	0.08
	After Operation	0.4	0.2	0.1	0.04	0.7	0.3	0.2	0.3	0.8	0.01	0.2	0.5	1.2	0.1
Corrected Vision	Before Operation	1.2	0.9	1.0	0.1	1.2	1.0	0.9	0.6	1.2	0.03	0.9	1.2	1.2	0.2
	After Operation	1.2	0.8	0.9	0.4	1.2	1.0	0.8	0.7	1.2	0.05	1.0	1.2	1.2	0.2
Refraction (in diopters)	Before Operation	3.25	14.0	7.0	14.0	2.0	7.0	8.0	6.0	3.0	10.0	5.5	4.0	1.25	11.0
	After Operation	1.75	11.0	5.5	9.0	0.87	3.75	6.0	2.25	1.0	7.0	3.5	2.0	0	6.0
	Reduction Caused by Operation	1.75	3.0	2.0	5.0	1.12	3.25	2.0	3.75	2.0	3.0	2.0	2.0	1.25	5.0
Reduction in the main meridian with high degree by combination of astigmatism (increased astigmatism)				2.5				3.0	3.0 (0.75)						
No. days after operation		34	40	56	24	131	44	22	36	64	20	88	59	100	37

TABLE 1
EFFECT OF THE TREATMENT MEASURED OBJECTIVELY

15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	Mean
3.0	9.0	6.0	2.0	3.0	4.0	4.5	3.0	2.5	8.0	11.0	5.0	4.5	10.0	3.0	3.0	4.0	6.0	
1.0	7.0	3.5	1.0	0.5	1.0	+0.5	0	1.0	4.0	8.0	+0.5	1.0	6.0	+0.5	0.5	+0.5	+1.0	
2.0	2.0	2.5	1.0	2.5	3.0	5.0	3.0	1.5	4.0	3.0	5.5	3.5	4.0	3.5	2.5	4.5	7.0	3.0
2.0	4.5	3.5		2.5	4.0	6.0		1.5	4.0	2.0 (1.0)	6.0	4.0 (0.5)	6.0	4.0 (0.5)	3.0		7.0	3.9
79	42	34	20	33	37	26	30	69	34	27	61	63	22	33	27	21	26	17-124

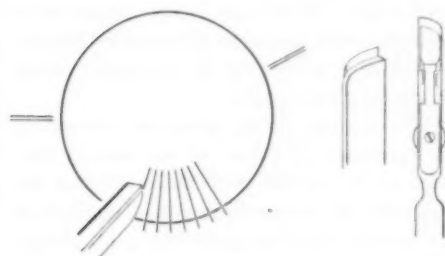


Fig. 10 (Sato, Akiyama, and Shibata). The anterior or superficial incisions. The picture at the right shows the Okamura knife.

Pressure bandages are not used, but a Hess protecting board is placed over the eye. Penicillin, sulfonamides, and vitamin A are administered externally and internally for two weeks. Atropinization is maintained for one week. Refraction and visual acuity are recorded four weeks postoperatively.

Within two months the refraction becomes stable, and only fine radial linear opacities may be seen under strong focal il-

lumination in a dark room, but they are not apparent under ordinary illumination.

IV. RESULTS AND DISCUSSION

Anterior and posterior half-corneal incisions were studied in 32 cases of myopia. They have caused a reduction of myopia, objectively measured from 1.5D. to 7.0D., with an average of 3.0D. Subjectively, the diminution was from 1.12D. to 6.0D., with an average of 2.8D.

In the meridian of maximum curvature in the cases with combined astigmatism, the reduction of refractive power, on the average, was 3.9D. objectively, and 3.5D. subjectively.

Included in this series were cases of relatively low myopia in which a minimum procedure was carried out. We feel safe in saying that eyes with four diopters of myopia can be made emmetropic, or so nearly so that only slight correction is necessary to acquire fully corrected vision. The results, de-

TABLE 2
EFFECT OF THE TREATMENT MEASURED SUBJECTIVELY

15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	Mean
0.2	0.09	0.1	0.2	0.1	0.05	0.06	0.1	0.4	0.04	0.08	0.1	0.1	0.02	0.4	0.1	0.1	0.1	
0.9	0.1	0.4	1.2	0.7	0.9	1.2	0.9	1.2	0.3	0.2	1.0	1.2	0.2	1.2	1.0	1.0	0.8	
1.2	0.3	0.9	1.2	1.0	1.2	1.2	1.0	1.2	0.7	0.5	1.0	1.2	1.0	1.2	1.2	1.2	1.0	
1.2	0.5	1.2	1.2	1.2	1.2	1.2	0.9	1.2	1.0	0.6	1.0	1.2	1.0	1.2	1.2	1.0	0.8	
2.0	7.0	5.0	2.25	3.0	4.25	4.0	3.0	1.12	10.0	11.0	4.0	3.0	11.0	2.0	2.0	3.0	4.5	
0.5	4.5	3.25	0.5	1.0	1.0	0	0	0	5.0	7.0	0.5	0	5.0	+0.5	0.5	0	0	
1.5	2.5	1.75	1.75	2.0	3.25	4.0	3.0	1.12	5.0	4.0	3.5	3.0	6.0	2.5	1.5	3.0	4.5	2.8
				2.5 (0.5)			4.0		5.0		4.5							3.5
86	44	56	90	40	44	26	30	92	73	40	55	56	41	30	28	21	22	20-131

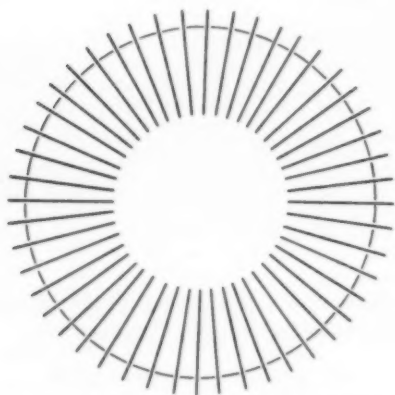


Fig. 11 (Sato, Akiyama, and Shibata). About 40 anterior half-corneal incisions are performed. In a case of mild myopia, fewer anterior incisions are made. If there is combined astigmatism, the anterior incisions are increased in the quadrants containing the highest degree of myopia. (See Figure 9.)

scribed in the last half of Table 2, of the cases which were treated with acquired experience, show these improvements as facts.

Concerning unaided vision, all cases were distinctly improved, and 20/20 vision was obtained in nine cases. In the 12 cases following Case 21, there were nine cases which showed no more than 4.0D. of myopia before treatment; eight of them became emmetropic, that is had 20/20 unaided vision, and one of them almost emmetropic.

The results of the operation have been observed in some cases for five months, and no remarkable diminution of the effect has been observed. Sustained reduction in refractive power in experimental animal eyes was similarly permanent.

We consider that this procedure, if properly performed, will safely cure myopia up to four diopters, and will produce marked improvement in myopia of from five to six diopters. This treatment, therefore, is efficacious for 95 percent of the myopic cases in Japan, since statistical studies⁷ on my-

opia conducted by Sato and others among the Japanese people show this percentage to have myopia of six diopters or less.

It is believed that additional experience will provide improvements in technique, as well as uniformly better results regarding the total dioptric reduction of myopia. In animal eyes, for example, a maximum hypermetropization of 18 diopters has been obtained with an average of eight diopters. No detrimental effects from this procedure have been observed, and none of the cases demonstrated any worsening of refractive error or loss of visual acuity.

The rationale of the operation is based on the increased curvature of the incised portions of the cornea, with the result that the curvature of the pupillary area of the cornea is lessened. Interestingly enough, this change of cornea was easily seen grossly in the rabbit's eyes in which a high degree of hypermetropization was effected by this procedure.

V. CONCLUSION

Thirty-two cases of myopia have been treated by anterior and posterior half-corneal incisions, with improvement ranging from 1.5D. to 7.0D., depending on the distribution and number of incisions made. In this series, an average of three diopters' reduction of myopia was obtained. All cases demonstrated remarkable improvement of unaided visual acuity.

This new surgical approach is a proven, safe method which definitely cures or adequately alleviates over 95 percent of all cases of myopia in Japan. Emmetropia is a professional necessity for many myopes, and this may be accomplished by the method described. Binocularity may be attained in cases of severe anisometropia, providing surgery is confined to the myopic eye.

Juntendo Medical College.

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ANOMALOUS PROJECTION*

ITS INCIDENCE, FACTORS IN DEVELOPMENT, CHARACTERISTICS, TESTS, AND TREATMENT IN 146 SURGICALLY TREATED STRABISMUS CASES

NORMAN S. JAFFE, M.D.
Miami, Florida

DEFINITIONS

Anomalous correspondence has also been referred to as abnormal correspondence, anomalous projection, and false macula. The word retinal is often inserted.

Swan¹ defines it as "an anomaly of binocular vision in which areas in the two retinas normally having a common visual direction acquire an unstable and often variable visual direction in relation to each other but usually in accordance with the squinting position."

Verhoeff,² aware of the many misconceptions concerning this phenomenon, went to great lengths to establish exact definitions. He offered that "a visual axis is defined as any line in external space, all suitable objects centered on which have their retinal images centered at the same retinal point. Corresponding visual axes are defined as any two visual axes that as visualized from their respective eyes with the aid of suitable objects appear to coincide. The imaginary line in which they thus appear to coincide is termed a binocular visual axis. Corresponding retinal points are defined as the retinal optical terminals of a pair of corresponding visual axes."

Verhoeff considered the terms anomalous correspondence, abnormal correspondence,

and false macula misleading. He felt that only one type of correspondence could exist, that is, the normal kind. When this condition does not prevail, there is no correspondence present. The fovea of the fixing eye has no functional counterpart in the strabismic eye in these cases. Since correspondence is non-existent, it is senseless to speak of abnormal or anomalous correspondence.

We know that, when the fovea of one eye is exposed to a light, the fovea of the other, although not exposed, will be aware of the after-image. This awareness of a contralaterally induced after-image requires that correspondence be present. When the normal system is absent, the unexposed eye is not aware of an after-image at the fovea or any other point on the retina. There is no binocular integration and correspondence is non-existent.

When this test was given to 71 patients with noncorrespondence, there was not one exception to these findings.

This is the most simple test I know for determining the existence of correspondence:

Expose one eye to a vertical bar of light for 20 seconds while the other eye is occluded. Then cover the exposed eye and allow the occluded eye to gaze at a light surface. If correspondence exists, the subject will report a vertical after-image. He will report nothing if correspondence is nonexistent.

* From the Department of Ophthalmology, U. S. Army Hospital, Fort Campbell, Kentucky.

This investigation merely confirms Verhoeff's theory. He used the term anomalous projection, not because he preferred it, but because he felt it was the most nearly correct of those in common usage.

In the normal state each retinal receptor has a local sign which distinguishes it from other retinal receptors. Each retinal point is functionally, although not anatomically, related to a corresponding point on the other retina.

In the infant, this relationship is weak and easily upset. The system requires experience to attain its full value. Once established it is not easily disturbed.

Objects in space are projected on a line emanating from an imaginary globe between the two eyes. Duke-Elder³ states that this cyclopean eye is farther back and slightly closer to the master eye.

INCIDENCE OF ANOMALOUS PROJECTION

There is much confusion concerning the incidence of anomalous projection in concomitant strabismus.

Enos⁴ reported that of 295 strabismics, 47 percent showed anomalous projection. Of 227 esotropes, 123 or 53 percent had anomalous projection, while this was present in only 10 or 16 percent of 66 exotropes.

Sugar⁵ quotes the results of the following investigators. The incidence of anomalous projection according to Hine was 71 percent, Fischer 50 percent or more, Bryant 50 percent, Muegge 61.5 percent of alternating and 27.4 percent of monocular squints, Travers 40 percent of those with good vision in each eye.

Casari⁶ used the diplopia test, Maddox-rod, and after-image test on 90 strabismics. Of 53 monocular esotropes, 33 showed unharmonious anomalous projection and 14 harmonious anomalous projection, an incidence of 90 percent. Only six or 10 percent had correspondence. Of 16 patients with monocular exotropia, eight had unharmonious and six harmonious anomalous projection (88 percent). Only one had correspondence and in one the presence of corre-

spondence could not be determined. Of 15 alternating squinters (esotropes and exotropes) five had correspondence while eight had harmonious and two unharmonious anomalous projection.

Strazzi⁷ used the diplopia and after-image tests on 80 strabismics: 65 percent of the 60 monocular strabismics (52 convergent, seven divergent, one sursumvergent) showed anomalous projection (80 percent, unharmonious; 20 percent, harmonious). Of the 20 alternators (17 esotropes and three exotropes) 14 had correspondence and six had anomalous projection. This is not in accordance with other reports.

Our results show that among 146 strabismics tested, there were 86 monocular esotropes; 32 cases or 37 percent had noncorrespondence. Of 12 monocular exotropes, three or 25 percent had noncorrespondence. There were 32 patients with alternating esotropia; 28 or 87.5 percent had anomalous projection, while eight or 50 percent of 16 alternating exotropes had noncorrespondence.

FACTORS IN DEVELOPMENT OF ANOMALOUS PROJECTION

When squint occurs, projection is in error by an amount equal to the deviation. To correct this error an anomalous projection system adapted to the angle of squint develops. If the shift of projection equals the degree of deviation, binocular projection becomes correct in spite of the squint. The need for amblyopia becomes unnecessary.

It is puzzling, however, that a shift of projection not adapted to the angle of squint (unharmonious anomalous projection) is so common. There is no wisdom in this. The projection is not "corrected." Amblyopia is as common in these as in strabismics with correspondence.

Probably the most important factor in the development of anomalous projection is the age of onset of squint. As already stated, a system of correspondence requires experience for its full attainment. The earlier the onset, the more readily is the system upset.

TABLE 1
RESULTS IN 48 CASES OF STRABISMUS WITH ANOMALOUS PROJECTION

Type	No. Cases	Average Deviation Prism Diopters	Correspondence Normal	No Correspondence
Esotropia alternating	18	42	8	10
Esotropia monocular	21	37	11	10
Exotropia alternating	6	46	5	1
Exotropia monocular	3	40	3	0
TOTAL	48		27	21

This explains why anomalous projection is less common in exotropes than esotropes.

Generally, exotropia occurs after correspondence has been established. The only exception to this is the group of intermittent exotropes who show Grade III fusion when the eyes are straight and then display anomalous projection adapted to the angle of squint when one eye turns out.

Another factor felt by some to be of importance is the degree of squint.

Scobee⁸ says "abnormal retinal correspondence is seldom found . . . in patients with very small angles of deviation, that is five degrees or thereabouts. Patients with large angles of deviation, that is, over 35 degrees, usually have normal retinal correspondence and less suppression than those with smaller angles."

The reason for this, of course, is that with large deviations the separation of double images is so great that they are not disturbing.

Jampolsky⁹ has refuted this concept with his investigation of 84 cases in which there was monocular strabismus of less than 15 prism diopters, a relatively stable angle of squint and slight amblyopia. In over 90 percent of these, he found an anomalous projection. He felt that many of these cases were formerly overlooked because "the dissimilar haploscopic targets of the usual size were too gross for the detection of a small angle of anomaly." He used small targets.

Burian,¹⁰ while agreeing that such cases certainly exist, stated that most small angle deviations are accommodative in nature and in these normal correspondence is prevalent.

I agree with Burian although there are many cases such as Jampolsky describes. They are resistant to orthoptic and surgical treatment. Among nine of my cases of monocular esotropia of less than 30 prism diopters, harmonious anomalous projection, and little or no amblyopia, only one was successfully operated on. A recession of one medial rectus was performed in each case. The other eight showed a return of the original deviation. This will be referred to later.

If the strabismus is of gradual onset with little inconvenience to the patient, anomalous projection is likely. In strabismics with a fixed angle of deviation it is also likely. When onset is sudden (as in noncomitant strabismics), correspondence is retained. Intermittent squinters also retain correspondence. The exception to this is the group of intermittent exotropes referred to above.

Stephenson¹¹ felt that the home background may be an important factor in the development of anomalous projection. Many of his patients were neurotic individuals who came from difficult homes. The parents were usually very nervous.

CHARACTERISTICS OF ANOMALOUS PROJECTION

We have already stated that the system of correspondence in infancy is unstable. It requires experience for its full attainment. If squint develops, a secondary system of correspondence may be acquired. The fovea of the fixing eye is functionally related to an eccentric retinal area of the deviating eye. If surgery under- or overcorrects the deviation, a tertiary system may develop.

Some patients may retain two or three systems at one time. If each retinal receptor has two or three local signs, monocular diplopia or even tripplopia is possible.

The subjective angle shows great variability. It may change from moment to moment and from test to test. It is difficult to imagine that a real system of secondary correspondence can exist. In the normal state, each retinal receptor is functionally related to one retinal receptor in the other eye.

In secondary correspondence, the fovea of the fixing eye is related not to one point but an area of points in the other retina. Verhoeff² considers this to be noncorrespondence. After-image studies indicate that there is no relationship whatsoever between the retinas.

The only wise arrangement of secondary correspondence would be one in which the projection was completely corrected. This is harmonious anomalous correspondence. Of what value is an anomalous angle of, let us say, 15 degrees in an esotropia of 30 degrees? It doesn't lessen the need for amblyopia. Indeed, amblyopia is less frequent in harmonious cases while in unharmonious cases it is just as frequent as when correspondence exists.

The magnitude of the anomaly may show extreme variability. There may be frequent oscillations between correspondence and noncorrespondence. It is not uncommon to find noncorrespondence for near and correspondence for far and vice versa. The explanation is probably to be found in the fact that their binocular stimulus was mainly for near in the first case and for far in the second case.

Lyle and Jackson¹² commented on a group of patients with about 35 degrees of esotropia. These showed an angle of anomaly of only about 15 degrees (subjective angle 20 degrees). Ordinarily we would expect a much larger angle of anomaly, say 25 degrees or more. They theorize that perhaps most of the binocular stimulation responsible for the anomalous projection occurred for the most

part at close range (13 inches).

Lyle and Jackson offered further evidence that anomalous projection is a binocular condition. They showed that, if a patient fixes centrally with the esotropic eye, the non-deviating eye will turn in the same amount that the other eye was turned. The corneal reflex will be eccentric in the usually non-deviating eye. On the major amblyoscope, the lion will still be in the cage. Thus, anomalous projection is not the fault of the usually deviating eye alone.

In strabismus, we are concerned with two types of suppression. In the case of esotropia, the false image of the object regarded is easily suppressed since it strikes an area on the nasal portion of the retina where the acuity gradient is low.

The other type of suppression is that of the retinal optical terminal of the visual axis which corresponds to the central visual axis of the nondeviating eye. This is the fovea. The first type of suppression prevents diplopia while the second type prevents confusion.

When correspondence exists, there is a small area of suppression confined to the fovea. When there is no correspondence (anomalous projection), the area of suppression is much larger and is in line with an eccentric portion of the deviating retina.

Travers asserts that the size of the scotoma is roughly proportional to the angle of anomaly. As the anomaly diminishes so does the size of the suppression scotoma.

It is well to add that the so-called "false macula" has none of the characteristics of the true macula except insofar as it acts as the projectional center in the deviating eye.

TESTS FOR ANOMALOUS PROJECTION

1. AFTER-IMAGE "TRANSFER" TEST

This test has already been referred to. It is the most sensitive of all tests. If one eye is exposed to a stimulus and the other eye is not aware of the after-image, there is a loss of binocular integration.

This test was performed on 48 alternating

strabismics. Of the 36 with anomalous projection, none was aware of the contraocularly induced after-image. Of the 98 monocular strabismics, all 35 with anomalous projection showed this absence of awareness.

This test is so simple it can be used on any individual. It does not require above-average intelligence or much concentration. The patient is not asked to judge distances. This test, of course, only signifies that correspondence is suspended; no estimate of the anomaly is given.

2. SCREEN TEST

Verhoeff² considered this the best test. The squinter is asked whether or not an object which he is fixing at a distance of six meters appears to change its position or to move when a cover is quickly transferred from one eye to the other.

Verhoeff states, "If, as is usually the case, the object appears unchanged in position, anomalous projection obviously exists, for the primary visual axes do not correspond. This is also true if, as determined by a suitable prism, apparent change in the position of the object differs from the angle of strabismus by as much as 10 prism diopters."

Of course, a person with straight eyes will report little or no apparent movement.

Before proceeding to the other tests, they first will be criticized. The following tests (major amblyoscope, Maddox-rod, and so forth) introduce conditions so abnormal that the results obtained with their use are often difficult to interpret or to correlate with the ordinary visual phenomena of normal persons or of squinters.

The simpler the test and the more natural the conditions, the more reliable and trustworthy it is.

With these tests, the fovea of one eye is presented with an image, while the fovea or eccentric retinal area of the other eye is given an image of a different kind. In the case of the Maddox rod, they are different images of the same object. With the major

amblyoscope, there are two different objects (lion and cage). The same may be said of the after-image test advocated by Bielschowsky.¹³

In normal vision every object in the binocular field is imaged on both retinas. If the strabismic reports that the two different objects are separated laterally in space, there is certainly anomalous projection, but the amount of separation cannot accurately be measured by any means because of the inadequate monocular criteria of distance in at least one eye.

The conditions are unusual and there are inadequate criteria of distance in each eye. For example, as Verhoeff² pointed out, with the Maddox-rod test, the subject may state that the two images appear separated laterally, but he is unable to state positively which is to the right of the other.

The same holds true for the vertical prism test. Anyone who has used these tests has been confronted at one time or another with this phenomenon.

3. MAJOR AMBLYSCOPE

The tubes of the synoptophore or troposcope are adjusted until there is no movement of the eyes when the charts are alternately illuminated. This represents the objective angle of squint.

The patient then adjusts the tubes until the lion is in the cage. This is the subjective angle. The difference is the angle of anomaly. Frequently, the lion will approach the cage, then disappear only to appear on the other side. We may use the point of disappearance or appearance on the other side as the measure. This test is difficult when amblyopia is profound.

4. BIELSCHOWSKY AFTER-IMAGE TEST

Actually, this test is attributed to Bielschowsky, Hering, and Tschermak. One eye is exposed to a vertical bar of light at a distance of two feet for about 10 seconds. This eye is then occluded and the other eye is exposed to a horizontal bar of light.

When correspondence is present, a perfect cross will be formed. This test is unreliable in amblyopes. It was shown¹⁴ that amblyopes fixate with areas one to three or four degrees eccentric to the fovea. Thus, the vertical bar is presented to the fovea of the good eye, while the horizontal bar is presented to an eccentric area. If correspondence exists, a perfect cross will not be formed. I never use this test on amblyopes.

5. VERTICAL PRISM TEST

A red glass and a vertical prism base-down are placed before one eye. Nothing is placed in front of the other eye. The object used is a light source at 13 inches or 20 feet. The subject will report the red light higher than the white and to the left or right.

With the use of a Risley prism before one eye, the images are adjusted so that the red light is directly over the white light. This is a measure of the subjective angle. Compare this with the objective angle of squint. The phorometer is an ideal instrument for this test.

There are other tests, such as the Tschermak congruence test, Lancaster red-green test, and Travers' mirror-screen test. The principles are similar. In the after-image screen, and Lancaster red-green tests the stimuli are foveo-foveal. In the vertical prism and Maddox-rod tests the stimuli are foveo-perifoveal.

TREATMENT OF ANOMALOUS PROJECTION

Scobee¹⁵ reluctantly reported his results on a small series of 13 cases with anomalous projection on whom surgery was performed. None received any preoperative orthoptics.

Postoperatively the eyes appeared straight in all 13 cases. In no case was postoperative diplopia present for more than three days. No postoperative therapy of any kind was given. Of the 13 patients, 12 developed correspondence one month postoperatively. My own results will be added to this group.

Scobee stated, "... if reasonably good

surgical alignment of the optic axes can be obtained, the majority of patients will receive enough orthoptic exercises in their every-day life by the simple expedient of opening the eyes in the morning on awakening and keeping them open all day to stimulate the redevelopment of normal retinal correspondence."

Scobee, however, felt that the ideal management is preoperative and postoperative treatment of anomalous projection. Apparently, he was not too certain about the latter statement before his unfortunate passing.

In the early cases, straightening of the eyes is all that is necessary to restore correspondence. In well-developed cases of anomalous projection, occlusion of the fixing eye is used in monocular squinters. The purpose of this is to break up the binocular stimulus for anomalous projection.

The vision of the covered eye should be tested at frequent intervals to prevent amblyopia. In a six-year-old girl with monocular esotropia, vision dropped from 20/20 to 20/70 in 10 days. Occlusion should be tried for one month before abandoning it.

Orthoptic exercises are given during the period of occlusion. The following methods are used:

1. *Massage of the macula.* The squinting eye fixes a bird while the cage slide is passed back and forth over the macular area. If the objective angle is 40 prism diopters, set the tubes at half the angle, 20 prism diopters, and move it to 60 prism diopters. It is well, in esotropia, to stimulate the macula from inside the angle, while in exotropia from outside. Of course, the pseudomacular area at 0 is to be avoided.

2. *Alternation.* Set the tubes of the major amblyoscope inside the angle in esotropia and outside the angle in exotropia. For example, if the objective angle is 40 prism diopters, set the tubes at 20 in esotropia and 60 in exotropia. The poorer eye is aided by increasing the illumination on its chart and by having it look at the larger object (cage). The patient is asked to look back and forth

from the bird to the cage. Again avoid the false macula.

3. *Oscillation.* Lock the tubes at the angle of deviation to stimulate the true macula. Move the tubes fast enough so that the subject can project the targets in the same direction. He must see the bird in the cage. After awhile the speed may be reduced until none is needed.

4. *Flashing.* This is done at the angle of deviation to stimulate the true macula. Adjust the amblyoscope to the exact angle of deviation and use pictures with fine detail requiring 20/40 vision.

The light is flashed on and off so that one picture is illuminated when the other disappears. The speed of flashing is increased until the after-image of the first continues during view of the second. Thus the two images which were separated by false projection are appreciated. Finally, one composite picture will be seen.

When fusion is appreciated, both lights are left on for a second or two and the images will separate. The patient will later be able to hold fusion for one minute and longer.

Preceding orthoptics, occlusion should be attempted to restore as much vision as possible. Orthoptic training is usually fruitless if vision is 20/100 or worse.

These exercises are usually useless in congenital squints with well-developed anomalies. The results in adults are likewise poor.

In obligatory eccentric fixation, orthoptic training is useless. Surgery should be done. It seems reasonable, also, that orthoptic therapy is best if the eyes are straightened surgically and the greatest possible visual acuity restoration has been achieved. I consider preoperative orthoptic training a waste of time.

Lyle and Jackson¹² suggest that if the angle of anomaly is over 10 degrees, operation should be done first. Many outstanding observers have cast orthoptics aside completely. Travers¹⁶ has finally concluded that surgery should be done immediately in

the treatment of anomalous projection.

There are many others who are pessimistic concerning the use of orthoptics in anomalous projection. Miss Mayou¹⁷ states that in "true" anomalous projection (her criteria are apparently very strict and there is a small percentage of "true" cases among all those with anomalous projection) orthoptic treatment is a waste of time.

Casari⁸ found that seven to eight percent of his patients achieved correspondence with orthoptic exercises alone; 25 to 33 percent of those treated surgically achieved this. Burian¹⁰ rightly criticized these findings, since Casari used only the stereoscope and the diploscope.

Jampolsky⁹ found that, in his cases of squint with small deviations, treatment of anomalous projection is fruitless.

At this point, I shall return to the question of surgery without orthoptics. All children under the age of nine years in my series received postoperative orthoptics. Surgery was performed on 48 adult strabismics with anomalous projection. These included soldiers and wives of soldiers.

¹⁸ The youngest patient in this group was aged 17 years, the oldest 38 years. The average age was 24 years. Good surgical alignment was achieved in 47 cases. The results shown in Table 1 were obtained 45 days postoperatively.

Scobee's figure of 12 out of 13 cases achieving correspondence with surgery alone, while remarkable, would not be too unusual if his patients were children. In my series, 27 adults achieved correspondence out of 48 patients. This is 57 percent. The most enthusiastic advocates of orthoptic therapy have never reported such a high rate of "cure" in adults. By "cure" we mean the attainment of correspondence, not alignment.

Note that of nine exotropes, eight achieved correspondence with surgery alone. This is not unusual when we consider that in most exotropes correspondence must have existed at one time and must have attained a relatively high degree of fixity.



Fig. 1 (Jaffe). A 21-year-old man with alternating exotropia. Objective angle: 48 prism diopters. Subjective angle: 12 prism diopters. A five-mm. recession of the left lateral rectus and a seven-mm. resection with three-mm. advancement of the left medial rectus were done. Grade III fusion postoperatively.

Slightly less than 50 percent of the 39 esotropes with noncorrespondence were "cured" by surgery alone. While I cannot prove it with this series, I am of the opinion that the institution of orthoptic therapy in this group would not have significantly altered the results.

Figures 1, 2, 3, and 4 illustrate typical cases.

There is one striking phenomenon in these results. The most difficult cases of anomalous projection were those with a relatively small objective angle of deviation. Of the 21 cases which did not achieve correspondence, the average deviation was 27 prism diopters while that of the "cured" cases was 49 prism diopters.

All cases were examined daily for the first 10 days postoperatively and then every second day for two weeks, then once weekly for two months.

Of the total of 48 cases with anomalous projection, there were 11 cosmetic failures. Again, it is interesting that eight of the 11 patients had an initial deviation of less than 35 prism diopters; five of the 11 returned to the original deviation within three days, one

required six days, and the other two failed after three weeks.

The other three failures are interesting. Their original deviations were 67, 62, and 53 prism diopters, respectively, measured by the cover test on the phorometer. While I usually pay little heed to the exact subjective angle, the measurements in these three, as determined by the vertical prism, red-glass, and Risley-prism tests, already described, revealed values between 10 and 20 prism diopters; two cases showed alternating esotropia and the other, a monocular esotrope with anisometropia and amblyopia (20/80).

At the first dressing the two alternators showed an overcorrection of at least 20 diopters. The eyes in the monocular case appeared straight at the first dressing. Within one week, all three showed an esotropia which measured between 26 and 30 prism

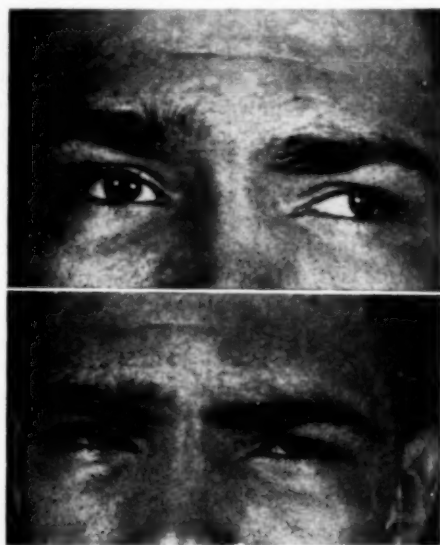


Fig. 2 (Jaffe). A 27-year-old man with alternating exotropia. Objective angle: 86 prism diopters, eight left hypertropia. Subjective angle: 20 to 26 prism diopters. A five-mm. recession of the right lateral rectus and an eight-mm. resection with three-mm. advancement of the right medial rectus were done. Following this, objective angle was 38 prism diopters. The same procedure with same measurements was done on the left eye. Objective angle: 0. No fusion.



Fig. 3 (Jaffe). A 25-year-old man with left esotropia. Objective angle: 42 prism diopters. Subjective angle: 16 prism diopters. A five-mm. recession of the left medial rectus and nine-mm. resection with three-mm. advancement of the left lateral rectus muscle were done. Grade III fusion postoperatively.

diopters. This is the angle of the optic nerve. They represent examples of the syndrome of Swan.

In this connection it might be noted this range of deviation, 26 to 30 diopters, was more frequent than any other range among 75 strabismics with correspondence. This deviation is indeed the happiest compromise in strabismus. Inhibition is not required since the optic nerve contains no retinal optical terminals. In addition, anomalous projection is not necessary.

A word on postoperative diplopia might be apropos. Of the 146 strabismics surgically treated, there was not one case of diplopia which persisted for more than four weeks. The diplopia which did occur was usually of very short duration, lasting from hours to days.

In most cases showing diplopia, the diplopia occurred in association with anomalous projection. This is not in line with the sug-

gestion of Posner and Schlossman¹⁸ that persistent postoperative diplopia usually occurred in patients with correspondence who were surgically overcorrected. They reason that a portion of the retina not previously suppressed now receives an image of the same object which stimulates the fovea of the opposite eye.

This explanation sounds plausible. Since in all of my cases the diplopia was of a fleeting nature, they should not be compared with those of Posner and Schlossman.

SUMMARY

Anomalous projection is accurately defined.

The reports of incidence by various investigators is discussed. My series consisted of 146 strabismics. There were 86 monocular esotropes of whom 37 percent had anomalous projection. Of 32 alternating esotropes, 87.5 percent had noncorrespondence. Of 12 monocular exotropes, 25 percent, and of 16 alternating exotropes, 50 percent showed anomalous projection.

Various factors in the development of anomalous projection are discussed. These include age of onset, degree of squint, ra-



Fig. 4 (Jaffe). A 19-year-old man with left esotropia. Objective angle: 36 prism diopters. Subjective angle: 0. A five-mm. recession of the left medial rectus and six-mm. resection of the left lateral rectus muscles were done. Objective angle: 0. No fusion.

pidity of onset, convenience to patient, and environment.

The characteristics of anomalous projection are discussed.

The tests for anomalous projection are discussed. A new test is presented and the existent ones criticized.

The treatment of this condition is discussed in detail, from nonsurgical and surgical viewpoints. Of 48 adults with anomalous projection in whom good surgical alignment was achieved by surgery alone, 27 spontaneously developed correspondence. The average deviation in these cases was 49 prism diopters while in those patients who retained

anomalous projection, the average deviation was only 27 prism diopters.

There were 11 cosmetic failures among the 48 cases with anomalous projection; eight of these had an initial deviation of less than 35 prism diopters. The other three had a much higher initial deviation and reverted to the angle of the optic nerve postoperatively.

The range between 26 and 30 prism diopters, the angle of the optic nerve, contained more cases in the series of 146 strabisms, than any other group.

There was not one case of persistent postoperative diplopia in the entire series.

1345 North Bayshore Drive (32).

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BLIND AND BLINDNESS: AN ETYMOLOGICAL NOTE*

THELMA G. CHAREN

Washington, D.C.

The eye has been the dominant organ of perception throughout time. The force of its import to human life is seen in the strongest phenomenal element of early religion, the sun, known in centuries of biblical and classical literature as the eye of day.[†] Just as light has the eye as its counterpart, the absence of light, darkness, has its correspondence in the absence of vision, or blindness. Since night, moreover, obscures vision, identification of loss of sight with darkness follows naturally. The purpose of this paper is to demonstrate that the etymological development of the words for blind and blindness consistently shows this theme of loss of vision as related to darkness.

In English, as in all Teutonic languages, the adjective blind appears to be related to an old verb *blandan* found in Old Saxon, Old High German, and Old Norse with the meaning "to mix" or "to confound."¹ From this word we derive also our words blend and blunder.² In Old Norse there is also *blunda*, to close the eyes, and *blundr*, slumber.

In Lithuanian the word *blandýti* means "to shut the eyes"; moreover, the third person singular verb *blendzia-s*, in reference to the sun means "to become dim."³ In Old Slavic the word for "make a mistake" is *blanditi*.

Throughout these languages, clearly, the common root form seems to carry the concept of darkness and confusion, thus darkness and confusion in the sight, and so, blindness.⁴

In Latin the common word for blind was *caecus*. This is from the ancient Indo-Germanic root SCA which meant basically a

covering, thus darkness.⁵ The original form of the Latin was probably *scaicus*, with subsequent loss of initial *s*, becoming *caecus*. The SCA root appears in the English words shade and shadow, in the Greek *σκιά* (*skiá*) and *σκότος* (*skótos*), shadow⁶ and in the Sanskrit *khâyâ*, shadow.⁶ The Greek form appears in medical terminology, particularly of roentgenology and ophthalmology, in the words skiagraphy, skiametry, skiascopy, ski-alytic, scotograph, scotoma, scototherapy, scotoscopy, and scotophobia.⁷

Caecum or cecum, the neuter form of the Latin *caecus*, appears in anatomy as the Latin translation of the Greek *τυφλόν* (*typhlón*) "blind gut," the name given in Hippocratic times to that portion of the intestines.

Dr. Edmund Andrews, the biomedical etymologist, comments, "The human organ deserves no such epithet. Such a term could only have arisen from the fact that anatomical knowledge came from dissection of lower animals which really have such an organ."⁸

In fact, the translation of the Greek above as blind gut is also that of the German *Blinddarm*, the word for cecum. An interesting sidelight is the use in classical literature of *vulnus caecum* (blind wound) and *ictus caecus* (blind blow) for one inflicted upon the back;⁹ in a medieval manuscript of about the twelfth century *cecus ictus* has been translated as a blow not causing bloodshed.¹⁰

Corresponding in usage to the common Latin word for blind, *caecum*, the Greek *τυφλόν* has a derivation related also to light and darkness from a different source. *Τυφλόν* is probably a shortened form of

* Current list of medical literature, Armed Forces Medical Library, Washington 25, D.C.

† The poetry of this metaphor extends to the common field flower, the daisy, literally, day's eye.

⁵ The root exists in a modified form in the name Horatius Cocles, who defended the bridge against Lars Porsena of Clusium in legend. Cocles, The One-Eyed, is from SCA and *oculus*, eye. (Lewis, C. T., *op. cit.*, p. 136.)

τυφελός (typhelós) from τυφώ (typho),* a verb meaning "smoke." Therefore the adjective would mean "smoked," that is, smoke-darkened, smoky, misty,¹¹ and hence, as above, blind. In addition to its use in medical terminology in reference to the anatomical cecum, typhlo- appears also in words denoting blindness. Dorland lists among other derivatives pertaining to the cecum: typhlitis, typhocolitis, typhlolithiasis, typhlopexy, typhlostomy; in relation to blindness: typhlolexia (word blindness), typhlogy (study of blindness), and typhlosis (blindness).¹² Both the Greek and Latin are represented in zoological nomenclature in relation to two families with vestigial or rudimentary eyes: Typhlopidae (reptilian) and Caeciliidae (amphibian).¹³

The Romance languages, by definition springing from the Latin, for the most part derive their words for blind and blindness

from *caecus*: Italian: cieco, cecità; Portuguese: cego, cegueira; Spanish: ciego, ceguera (or ceguera). Although the French uses the Latin *caecitas* (blindness) for its noun, cécité, the adjective form derives from *oculus*, eye, referred to in the note above: aveugle, that is, *aboculus*, *ab*, without, and *oculus*.¹⁴ It is from the French aveugle that we in turn in English derive inveigle, that is, to hoodwink or to blind a person to facts.

In a language as unrelated to the classical as Hawaiian, the same element of blindness as darkness also appears. The Hawaiian word for "blind in one eye" is *makaʔaʔa*; for "completely blind," *makaʔo*. The root *maka* is face or eye and *ʔaʔa* is tight, fast, or secure, that is, an eye shut tight forever; *ʔo* is night or dark or obscure, that is, both eyes obscured forever by darkness.¹⁵

Throughout its etymological development the word blindness is related to darkness. The physical loss of sight is so closely allied to the physical absence of light that the etymological metaphor as seen in the examples above is inevitable.

200 Rhode Island Avenue, N.E. (2)

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NOTES, CASES, INSTRUMENTS

GALACTOSEMIA AND GALACTOSURIA*

MATTHEW M. STEINER, M.D.
Chicago, Illinois

Galactosemia and galactosuria or galactose diabetes, as it is sometimes referred to, is a congenital metabolic anomaly resulting from an inability to metabolize galactose adequately.[†]

This syndrome is characterized by malnutrition, hepatomegaly, cataracts, occasional mental deterioration, and the laboratory findings of galactosemia, galactosuria, and albuminuria. While this abnormal metabolism of galactose has serious effects on growth and development, as well as upon the eyes, the process may be reversed if it is diagnosed early and galactose is removed from the diet.

CASE REPORT

History. This white male infant was delivered by section during the eighth month of gestation because of toxemia of pregnancy. This was the mother's first pregnancy and there was no history of familial diseases.

The child weighed 3.5 kg. at birth and the immediate postnatal condition was good. However, he took feedings poorly and seemed listless after the second day. Despite various changes in the formula, he did poorly and lost weight.

On the ninth day, jaundice appeared and lasted for three days. On the 10th day, examination of the urine disclosed a positive test for reducing substance as well as albumin. Subsequent examinations of the urine disclosed the same findings.

He did poorly at home, and during the fourth week, a large mass was found in the

right upper quadrant and he was hospitalized at Children's Memorial Hospital.

On admission, the pertinent findings were poor nourishment, listlessness, lamellar cataracts in both eyes, and an enlarged liver (five cm. below the costal margin). Dr. Gamble noted that the cataracts were the same in both eyes and involved a large portion of the center of the lens and the infantile nucleus. He concluded, therefore, that it occurred close to the time of birth.

The laboratory findings revealed a positive test in the urine for reducing substance and albumin. Qualitative tests of urinary sugar revealed negative Seliwanoff for levulose, negative Tauber for pentose, positive mucic acid test for lactose and galactose, and a positive Rubner test, which rules out lactose. Hence, the reducing substance in the urine was galactose. Plasma protein, cholesterol, and cholesterol esters were normal. Prolonged prothrombin time and positive cephalin flocculation test indicated some liver damage. There was a moderate anemia.

Glucose tolerance tests, at this time, revealed very high values due to the high blood galactose levels.

On the 13th hospital day, the patient was placed on a mull-soy formula (mull-soy is a lactose-free soy bean milk). At that time he weighed the same as on admission—3.5 kg. A prompt gain in weight occurred. Within three days, reducing substance disappeared from the urine and on the fifth day of this regime, the albuminuria was gone.

Glucose tolerance tests after treatment showed almost normal values. Adrenalin and insulin tolerance tests gave normal values.

On the 17th day, edema appeared and responded to plasma and blood. The total protein was 3.3 gm. percent at this time and rose to 4.5 and 6.12 gm. percent.

On the 27th day, the infant was again placed on an evaporated-milk formula containing lactose and the laboratory tests were repeated. The weight was 3.9 kg. In 24 hours,

* Presented before a joint meeting of the Chicago Ophthalmological Society and the Chicago Diabetic Association, May, 1952.

† Langewisch, W. H., and Bigler, J. A.: Disorders of glycogen metabolism. *Pediatrics*, 9:263 (Mar.) 1952.

galactose appeared in the urine and five days later albumin appeared. The cephalin flocculation test and prothrombin test became abnormal. The weight dropped to 3.6 kg.

He was again placed on a lactose-free formula—Nutramigen—and gained 0.2 kg. in one week. Again the galactose, as well as the albumin, disappeared from the urine. At this time the liver was still enlarged to five cm. below the costal margin. The cataracts were still extensive. He was discharged on a Nutramigen formula with banana and cereal, after one and one-half months in the hospital.

In February, 1952, when the child was again hospitalized for evaluation, several definite changes were noted. At 14 months he weighed 18.5 pounds; he was alert, sat and stood up and seemed normal mentally.

Dr. Gamble found, on ophthalmic examination, that each lens showed a vague refractile ring which corresponds to the edge of the lens nucleus. It was refractile rather than opaque. It was much less evident than previously, although it seemed larger because the nucleus was larger. The liver edge was just below the costal margin, in contrast to five cm. below at the time of discharge in June, 1951.

Galactose tolerance tests showed better tolerance: fasting: 0; at one-half hour, 50; at one hour, 124; at two hours, 137; at three hours, 169. Cephalin flocculation was one plus. Total protein, albumin, and globulin were normal.

DISCUSSION

Infants with galactosemia appear to be normal at birth and for a few days afterwards. There is no icterus, hepatic enlargement, or signs of portal obstruction until milk has been ingested for several days. It seems apparent that there may be a quantitative variation in the severity of the defect of galactose metabolism. With complete or nearly complete inability to metabolize galactose, death may occur within a few days after birth. Others, who survive, can apparently metabolize some galactose but usually are

severely malnourished by the time they reach the age of two or three months.

The case presented here showed most of the cardinal findings: poor nutrition and poor weight gain, cataracts, hepatomegaly, galactosuria, and albuminuria. Edema may be marked and cases have been reported with ascites.

Laboratory studies show increased prothrombin time, decrease in plasma proteins, positive cephalin flocculation, abnormal bromsulfalein retention, and intolerance to galactose.

High levels of reducing substance are present in the blood, the greater part of which is due to galactose. The oral galactose tolerance tests show a high prolonged curve of nonfermentable reducing substance (galactose) accompanied by a simultaneous fall in fermentable reducing substance (glucose).

Concerning the pathogenesis of galactosemia—the liver is infiltrated with fat as a result of an inability to metabolize galactose normally. It has been suggested by Bell and others that this is comparable to the situation in poorly controlled human or experimental diabetes, where the abnormal metabolism of glucose is often associated with fatty infiltration of the liver.

Distention of the hepatic cells with fat may have two secondary effects:

1. It can produce (a) intrahepatic biliary obstruction with jaundice; (b) intrahepatic portal venous obstruction with ascites, splenomegaly, and abdominal venous distention; (c) degeneration or necrosis of hepatic cells with scarring or cirrhosis.

2. The lipid infiltration of the liver interferes with hepatic function, as evidenced by positive cephalin flocculation and thymol turbidity tests, retention of bromsulfalein, and lowering of the plasma proteins and prothrombin. It is probable that, if the intolerance to galactose were not complete, the inability of the liver to metabolize the substance would be accentuated when hepatic function was diminished by the infiltration of fat. In other words, once the liver becomes

fatty, the galactosemia and galactosuria may be secondary reactions in part.

Prognosis in this disease depends upon the patient's age when the diagnosis is established. If severe liver, kidney, and brain damage is allowed to occur, the prognosis is poor; however, if therapy is instituted early in the course of the disease, the pathologic manifestations are reversible.

There is usually a prompt weight gain upon elimination of lactose from the diet. Hepatic function is improved and the size of the liver diminishes. The albumin and galactose disappear rapidly from the urine. Increased tolerance to ingested galactose may appear. The cataracts may disappear after several months, if therapy is instituted early in life.

Treatment of this disease consists of a lactose-free diet by using a milk substitute such as Nutramigen or soy-bean formula. A diet high in carbohydrate may also be important, for it has been shown experimentally to improve the galactose tolerance and to minimize the effects of small amounts of galactose unavoidably included in the patient's diet. In view of the excessive hepatic fat, choline might also be included in the diet.

6351 North Broadway (40).

FORCEPS-LOOP

FOR INTRACAPSULAR LENS EXTRACTION

EDWARD GROM, M.D.
Porlamar, Venezuela, S.A.

It is well known that sometimes during extraction of a cataract using the capsular forceps, complications oblige the use of the loop. That means, that at any moment during traction on the lens capsule, the forceps may miss contact with the lens. Once the ligament of the lens is broken it may be necessary to finish the extraction over the loop.

At the moment it is necessary to substitute the capsular forceps for the loop time is lost

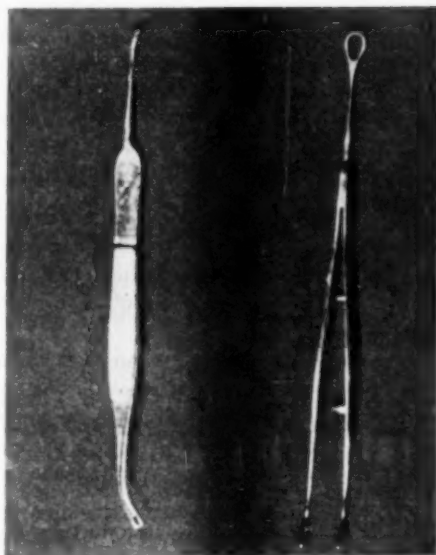


Fig. 1 (Grom). Front and side views of the forceps-loop.

in changing instruments. Also, this action causes the surgeon to lose, if not the visual control, at least his manual control over the area, especially over the partially extracted lens. In order to avoid that trouble, a combination of the excellent Arruga forceps and the Snellen loop was made.

The upper part of the loop was welded to the base of the forceps, care being taken not to turn up the ends of the forceps. If it is necessary to exchange forceps for loop, a rotatory movement of the forefinger will accomplish this.

Edo. Nueva Esparta.

Thanks are expressed to Mr. Alvaro Terren for making the instrument.

AN IMPROVED MUSCLE TUCKER

WILLIAM J. HARRISON, M.D.
Philadelphia, Pennsylvania

My first experience in muscle surgery was with the Todd tucker. This instrument in my inexperienced hands proved somewhat

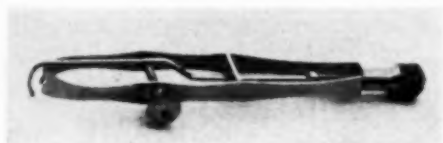


Fig. 1 (Harrison). An improved muscle tucker.

awkward and difficult to use. The tucker laid flat over the eye, and one needed dexterity and patience to obtain a sufficient tuck and added ability to introduce the suture through the muscle.

It occurred to me that, if an instrument was so constructed that it would lie in the perpendicular plane, one would have ample room to obtain a sufficient tuck and certainly the suture could be introduced in an easier fashion.

To facilitate the suture introduction, the tucker was made with a notch in either blade which produced a large enough opening for the passage of the needle and prevented injury to the sclera.

I still believe that this notch is the most important part of the instrument and while most tuckers today have this notch, I must claim priority for its introduction. Such an instrument was reported by me at the January, 1928, meeting of the College of Physicians, Philadelphia, and later reported in the *AMERICAN JOURNAL OF OPHTHALMOLOGY* of April, 1928.

This instrument consists of two principal parts: (1) The equivalent of a spring forceps, the blades of which may be approximated by means of the nut and threaded bar; (2) a hook, situated between the forceps blades and which may be raised or lowered in relation thereto by means of a nut shown at the upper extremity.

The instrument is applied perpendicularly to the muscle, with the crossbars forming its base squarely at right angles to the edges of the muscle. The hook is lowered sufficiently to be passed under the muscle, then, by means of the nut above, the hook is raised, drawing the muscle up between the blades

of the forceps and creating a tuck or loop.

When sufficient length of muscle has been drawn up, the forceps are closed by means of the nut at the side of the instrument, and the muscle loop is securely held while a double suture, guided by the notch at the extremities of the blades, is passed through the center of the muscle.

Advantages of the instrument are:

1. Simplicity of instrument, with resultant simplicity of operation
2. Easily sterilizable
3. Amount of muscle tucked easily seen
4. Notch in instrument prevents injury to sclera and permits easy introduction of the suture
5. Closure of the blades on the muscle tuck avoids traction when tying suture, giving a secure, tight knot
6. There is no interference by assistant's hands, as the instrument can be held by the distal extremity and the operator has free access to the muscle.

For sometime I have noted that occasionally one met up with a rather wide and somewhat thinner muscle so that, at the time of tucking, the muscles overhung the two blades, and it was necessary to loosen the center nut so that one might tuck that part of the muscle under while it was being tied. It was necessary to repeat the same procedure on the opposite half. To overcome this difficulty, the following improved tucker is presented (fig. 1).

You will note that the cross part of the blade now describes an arc which permits the muscle to bunch together so that the entire muscle is within the confines of the hook. This has proved quite satisfactory, and I believe it to be a definite improvement.

135 South 17th Street.

PROBABLE TOXOPLASMIC CHORIORETINITIS

MARTIN P. KOKE, M.D.
San Diego, California

Sabin¹ has stated that there is no evidence to show chorioretinitis can be a manifestation of toxoplasmic infection occurring at any time after the birth of the individual. Wilder² has found organisms with morphologic characteristics of toxoplasma in granulomatous chorioretinal lesions but, in reviewing the literature, points out that chorioretinitis has not been observed in mothers of infants with toxoplasmosis.

This report presents further evidence that toxoplasmosis may produce chorioretinitis in an adult.

A white woman, aged 25 years, was seen on July 27, 1945. She had noted poor vision of the left eye two weeks before the birth of a child on November 20, 1944.

External eye examination showed no abnormalities. With lenses, the vision was: R.E., 20/15; L.E., 20/400.

Ophthalmoscopic examination disclosed no abnormalities in the right eye. The left macula was occupied by an elevated, yellowish-gray lesion. On the summit of the mass was an irregular, dense, white cap. The superior portion of the lesion was dark gray and it appeared to be draped over the main body of the yellowish-gray tumor. Stria from the lesion radiated into the surrounding retina.

The ocular media were clear and no other lesions or abnormalities were noted in the eye.

On June 8, 1945, before seeing this patient I examined her daughter, aged six months, because the mother had noted the child's eyes were crossed and the right pupil looked gray. The child had ocular nystagmus, convergent squint, and slight ptosis of the right upper lid. She did not fix or follow a point light.

There were a few folds in Descemet's membrane and each cornea appeared small. The anterior chambers were very shallow and a few posterior synechias were present



Fig. 1 (Koke). Skull X-ray film taken when the child was aged six months.



Fig. 2 (Koke). Skull X-ray film taken when the child was aged eight years.

in each eye. No signs of active inflammation were seen.

Immediately behind the right lens and apparently in contact with the posterior capsule was a dense, grayish-white mass or membrane. There was no fundus reflex. A grayish-white mass occupied the entire temporal two thirds of the left vitreous cavity and, although a red reflex was seen from the remaining fundus, the detail was obscure. Skull X-ray studies showed intracranial calcification compatible with a diagnosis of toxoplasmosis.

The baby was a full-term child, weighing five pounds one ounce at birth. The mother did not have measles or any other illness during her pregnancy. The house in which she lived during her pregnancy had many rats and fleas. She and two older children were bitten many times by the fleas. The family had a fox terrier which had a skin disease.

In May, 1952, the serum of the mother was positive for toxoplasma antibodies in the titer of 1:256 and the child in the titer 1:64. According to Dr. H. A. Feldman, these serology data support a diagnosis of toxoplasmosis. The two older children (September, 1952) had no antibodies to toxoplasmosis. The mother has had a normal child since the one described.

The mother was last examined in August, 1952. The lesion of the left macula was less elevated and areas of pigmentation and depigmentation were present.

The child was last examined in September, 1952. She was in Pacific Colony State Hospital, an institution for mentally defective patients. Her head appeared smaller than normal. She had recurrent attacks of clonic spasms of her extremities. She was unable to sit alone and did not respond to visual or auditory stimuli.

The pupils did not react to light and she

did not fix or follow a light. The lens of the right eye was opaque. Posterior synechias were evident.

The cornea of the right eye was small and faintly cloudy. The pupillary portion of the iris appeared retracted. The intraocular pressure was normal to palpation.

The cornea of the left eye was small and a few grayish deposits were evident in the nasal and temporal portion near the limbus. A few posterior synechias were seen. The lens was grossly normal and a gray mass occupied the temporal half of the vitreous cavity. A red reflex was evident in the remaining fundus but details were obscure. The intraocular pressure was normal to palpation. There was an increase in the intracranial calcifications seen on skull X-ray studies.

SUMMARY

A case of chorioretinopathy in an adult, which may be due to toxoplasmosis, is presented. The evidence is clinical or circumstantial. Approximately two weeks after onset of the chorioretinal disease the patient delivered a child who had extensive intraocular disease, intracranial calcification, and positive serology for toxoplasmosis. The serum was positive for both mother and child seven years after the disease was noted.

The striking characteristics of the mother's lesion were: yellowish-gray color, elevation with radiating retinal stria, absence of vitreous opacities when first seen and when seen seven years later, absence of satellites. It was my impression that the lesion was a choroidal inflammatory mass which elevated and destroyed the overlying retina.

233 A Street.

I wish to express appreciation to Dr. George Tarjan of Pacific Colony State Hospital for permission to examine this child, and to Dr. H. A. Feldman for providing the serology examinations.

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SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

CHICAGO OPHTHALMOLOGICAL SOCIETY

May 19, 1952

DR. GLENWAY W. NETHERCUT, *president*

(A joint meeting with the Chicago Diabetic Association at the Chicago-Illini Union. The clinical meeting was presented by the Department of Ophthalmology, University of Chicago.)

HEMANGIOBLASTOMA OF RETINA

DR. DUVAL B. JAROS: Von Hippel's disease, or hemangioblastoma of the retina, emerged as an entity at the turn of the century, and less than 30 years ago its association with systemic hemangioblastomatosis was recognized. The disease has shown hereditary passage and is thought to be a result of mesodermal maldevelopment in the first or third month of fetal life.

Pathologically it consists of proliferation of hemangioblasts at one or more foci in the retina, and the clinical course follows logically the events attendant on the development of such a tumor.

The young endothelial cells forming the tumor have two potentialities: (1) To form capillaries and (2) to pass a transudate. Pursuant to the first property, a capillary net forms between two supplying vessels, and the vessels enlarge hugely in response to the new load. As a result of the second property, cystic spaces form in the tumor, and eventually the retina is split by dissecting transudates.

Back pressure through the dilated vein causes widespread changes—retinal exudates and edema, retinal hemorrhage, vitreous hemorrhage, clouding of the vitreous, and retinitis proliferans.

If untreated, the eye is invariably lost,

either through total detachment alone, or through glaucoma, or through direct extension with rupture of the globe.

Case Report. This 26-year-old white man noticed an inferior nasal scotoma in the left visual field nine months ago. When first seen in October, 1951, the scotoma was evident on examination and vision in the eye was 20/70.

Fundus examination revealed two huge vessels, arterial in color, coursing together from the disc to the equator at the 2-o'clock position, where they disappeared without branching into a small (1.5 disc diameters), elevated, round white mass. The vessels were six times normal size and were tortuous. The vein could be identified by its tributaries.

Some retinal traction folds and exudates were present along the course of the vessels. Early retinitis proliferans was evident, and the vitreous was slightly clouded. Neurologic examination and X-ray studies disclosed no Lindau's component.

— In December, two months later, vision was reduced to 20/200 and the scotoma included the fixation point. Fundus examination revealed progression of the damage with shrouding of the vessels in glial tissue, and the presence of frankly yellow transudate elevating the retina near the tumor. The tumor had not changed in size. Retinal exudates were more generalized.

In early January, three radon seeds, each two millicurie in strength, were sutured to the scleral coat over the tumor. They were removed 41 hours later, giving a calculated dose to the tumor of 4,500 r. Healing of the wound was satisfactory.

In subsequent examinations there was little change in the fundus picture for two months, then the vessels began to diminish in size until, at present, four months postoperatively, the artery is half its original size and the vein is reduced by one third. The tumor mass

seems unchanged, and its elevation is perhaps a little increased.

Tension in the left eye has consistently been a little higher than in the right, running about 23 mm. Hg (Schiotz).

CHORIORETINITIS AND PERIPHLEBITIS

DR. VERNON K. S. JIM presented a 36-year-old white woman, first seen in the eye clinic on February 1, 1950, with the complaint of foggy vision and a black spot in the vision of the left eye on lateral gaze, of three weeks' duration. The onset was spontaneous. Vision at this time: R.E., 20/20+; L.E., 20/10-3.

The patient's past history was essentially negative. The family history revealed that her mother developed blindness before death from nephritis at the age of 56 years; a grandmother became blind two years before death with etiology unknown.

External examination of both eyes showed normal findings. The corneas and anterior chambers were normal. Schiotz tension was normal.

Examination of the right fundus revealed an essentially normal right eye.

The left eye showed vitreous opacities and some clouding of retinal details. A large chorioretinal lesion was noted about two disc diameters below the disc, measuring about 2.0 by 2.0 disc diameters in size. The external area appeared white with a rim of black pigment in the periphery. Small exudates were noted around this lesion, especially in the area between the lesion and the macular area.

Complete laboratory examinations showed nothing of significance. There was a trace of albumin in the urine. Blood agglutination tests for typhoid, paratyphoid, tularemia, and brucellosis were negative. A chest microfilm was noted as negative. However, a full size chest X-ray film showed a small patch of faint clouding in the right apex with pleural thickening. This was interpreted as a minimal right apical lesion, presumably tuberculosis.

A daily temperature record revealed no abnormal variations. The skin tests to old tuberculin were positive; to brucellergen, Frei, Dipylidium caninum, Trichinella, toxoplasma, histoplasmosis, and coccidiosis the skin tests were negative.

The clinical impression at this time was a chorioretinitis of possible tuberculous etiology. The patient was hospitalized for two weeks and placed on streptomycin-PAS therapy (1.0 gm. of streptomycin and 8.0 gm. of PAS). No abnormal toxic effects were noted.

The edema of the lesions subsided and the satellite lesions decreased in size. When discharged two weeks later there was disappearance of the satellite lesions in the left eye.

The patient was seen at three-month intervals and remained relatively well until April, 1952, when she noticed blurring of vision in the right eye, seven weeks after having delivered a child.

Examination revealed a normal cornea and anterior chamber. Ophthalmoscopic examination of the right eye showed a periphlebitis of the superior nasal vein manifested by strands of white connective tissue and tortuosity of vessels. The chorioretinal lesion in the left eye appeared unchanged.

A chest X-ray study showed small calcific nodules in the upper one third of each lung compatible with an old minimal tuberculous lesion. There was no evidence of present activity.

Blood tests, urinalysis, and Kahn test gave negative reactions. Skin tests were positive to O.T. in 1:10,000 and 1:1,000 dilutions; other skin tests were negative.

It was decided to place this patient on isonicotinic acid hydrazide therapy—the new antituberculous drug. She is now receiving 50 mg. three times a day by mouth. Subjectively there has been slight improvement in the vision of the right eye. However, she has not been on this therapy long enough for complete evaluation.

Ocular tuberculosis is usually secondary to tuberculosis elsewhere in the body and

rarely primary in the eye. Also, patients with active tuberculous lesions in the body rarely show ocular involvement, whereas, apparently normal healthy individuals with healed tuberculous lesions frequently show ocular tuberculosis.

Involvement of the uveal tract may occur as a disseminated chorioretinitis, as seen in this patient. Clinically this cannot be differentiated from luetic or other types of unknown chorioretinal lesions.

Tuberculous periphlebitis usually occurs in young adult males. Whitish streaks are usually seen along the veins, most frequently in the periphery. If the periphlebitis is severe, retinitis proliferans may result which, in turn, may lead to localized retinal detachment. A serious complication is sudden loss of vision due to a massive vitreous hemorrhage.

OPHTHALMOSCOPIC CHANGES IN CHILDREN WITH DIABETES MELLITUS

DR. ARLINGTON C. KRAUSE: In 1941, Duke-Elder in his exhaustive encyclopedia wrote that diabetic retinopathy was rare under the age of 40 years. He could find only six reports at that time. The reason is that in the pre-insulin era, children did not live long enough to develop retinitis of any degree. Many times they died in a few months. With the prolongation of life with insulin, retinitis came later in life until now it is relatively common among children, adolescents, and adults with juvenile diabetes.

Since 1940, innumerable cases have been reported. Joslin, who studied diabetes for a lifetime, said "ocular complications in diabetes are frequent, distressing, and destined to become one of the challenging problems of the future." This statement is particularly true for juvenile diabetics who are now surviving through careful diabetic management. So we see a progressive increase in numbers of patients with diabetic retinopathy.

The observations and, accordingly, the

statistics on juvenile diabetes depend greatly upon the observer, the type of patient, the time, and the clinic. For instance, intelligent patients who are well controlled and are followed closely in a diabetic clinic for years give a better insight into the course of juvenile diabetic retinopathy than those followed in an eye clinic.

In the eye clinic children or adolescents with diabetic retinopathy are rarely seen. In contrast, many adult eye patients are found to be diabetic by means of urine and blood tests after their indicative fundus signs are observed. Some of these patients had juvenile diabetes.

In this discussion, I shall try to summarize the impression I have received from more than 100 cases of juvenile diabetes followed by the Metabolic and Pediatric Clinics at the University of Chicago. Patients with the onset of diabetes mellitus before the age of 15 years are considered to be juvenile diabetics. The amount of ocular damage seems to follow: (1) The severity of the disease; (2) the duration of the disease; (3) the degree of the control of diabetes.

In general, patients who require less than 60 units of insulin a day tend to have less severe retinal disease than those who require more. Furthermore, the disease tends to be seen later in life; however, this is not a close correlation. Children who have diabetes that is difficult to control may have severe and rapid retinal damage. Usually children who have diabetes when they are less than five or six years of age have less retinal damage than older children. This is apparently because of the ease of diabetic management in the younger child by parents and by physicians.

If large groups of juvenile diabetics are surveyed, it seems that the retinopathy is related to the duration of the disease. This is most apparent in unclassified cases. A good comparison cannot be made with unclassified cases because of too many variables. But it also is evident in cases which are rigidly controlled and in which there

is no other disease. A small number of good observers believe that the ocular disease has no relation to the duration of the diabetes.

There seems to be little doubt that the degree of control of juvenile diabetes is associated with the severity of retinal disease. There seems to be no time limit on the duration of good vision or prevention of retinopathy in diabetic patients under good treatment, and with proper cooperation, who are otherwise healthy.

A well-controlled patient may have moderately severe diabetes from childhood for 20 to 30 years without having any signs of damage to the lens or retina. A relatively few rigidly controlled patients will show signs of retinal damage in spite of treatment.

The retina may show microaneurysms and punctate exudates. The lesions are usually few and small.

In patients less rigorously controlled, the degree of retinopathy tends to vary with the treatment and diet. Of course, there is much overlapping of the degree of retinopathy in these patients in relation to method and kind of control. Other diseases, of course, have an influence on the course of diabetes. Pregnancy, kidney disease, hypertension, arteriosclerosis, infectious diseases, and, perhaps, heredity may modify the diabetic changes in the retina. It seems that the irregular course of juvenile diabetes is responsible for many problem patients with ocular disease.

The retinopathy in juvenile diabetes is quite uniform in most cases. Vision is almost always normal for many years with or without punctate hemorrhages. Vision is a relatively poor index of retinal disease.

Venous dilatation is the first visible sign in the retina. Punctate hemorrhages or microaneurysms are next seen, in or near the macular area, and sometimes far out in the periphery of the retina. Often they are obscure and may be difficult to see. They may precede the exudate by years.

White exudates in dots may accompany or follow the appearance of hemorrhages.

Evidently the deep punctate hemorrhage ends in a microaneurysm. The punctate exudate and hemorrhage may come and go even in severe diabetes. If the exudates become large and confluent it takes months and years for them to disappear. The punctate hemorrhages may disappear in a few weeks.

Both types of lesion may occur in spite of proper treatment. Commonly, they are seen 10 to 20 years after the onset of diabetes in the treated patient.

The venules and their connecting capillaries in the retina and on the disc may show dilatation, aneurysms, and sacculation. They are visible in a bright light with a polarized yellow-green filter. Transillumination may help to make them evident.

Striate or large hemorrhages occur late in the chronic disease or in the acute form. Usually by this time the venules and veins are affected. Iris vessels also may be visible. If exudate or hemorrhage passes the internal limiting membrane, retinitis proliferans and neovascularization may occur.

In partly uncontrolled severe juvenile diabetes, there is some evidence that a low intraocular pressure may result in dilatation of the veins and cause leakage of serum or blood from the damaged venous system. It has occurred unilaterally in eyes with the lower intraocular pressure in juvenile diabetes. Marked retinopathy with hemorrhages and proliferation of connective tissue may result in a scarred retina after treatment.

In some patients there seems to be an inherent tendency to become careless about diet and treatment. In some patients, when seen for the first time, the retinitis is mild in spite of a high blood sugar. The explanation is that the diabetes is of short duration.

Most clinics report a high frequency (13 to 16 percent) of diabetic cataracts in juvenile diabetes. We have seen less than five percent. Diabetic cataracts may occur in spite of closely controlled treatment. In the adult patient who has had juvenile diabetes, cataracts may appear earlier.

The argument has been advanced that the lens is predisposed toward cataract as a genetic variation or has been injured previously by a nondiabetic condition. Treatment of the diabetes in the early acute stage may prevent advancement of the lens changes or may reverse them.

Early strict treatment, a mild form of diabetes, and a young child are the favorable factors of treatment of lens disturbance.

The various conditions associated with diabetic retinopathy in children are: severity of the diabetes, long duration of disease, poor control, kidney damage, high petechial counts, high blood pressure, sclerosis of peripheral vessels, and poor health.

Rigid and constant control of the diabetes is the most important factor in the prevention and healing of the retinal lesions and, of course, prolongation of life of the juvenile diabetic. Proper treatment of the ocular diabetic lesions and prevention of blindness is mainly in the hands of the internist. The difficulty is that a patient with juvenile diabetes has a constant lifetime problem.

Discussion. Dr. Alvah L. Newcomb: I agree with Dr. Krause on practically everything he said except that I feel the management of a young diabetic is not easy. These patients may have hypoglycemic reactions or it may not be possible to control the glycosuria.

One type of diabetic with a pathologic condition of the eyes not mentioned is the infant of a diabetic mother. We have had about 20 such infants and, of those, three had squint, two divergent and one convergent squint. I do not know why squint occurs unless it might be because of severe anoxia, which occurred in two of these cases. In more than 250 children that I have seen, only one was found who developed cataract early. That child had had undetected diabetes for a year. He also had hemochromatosis, and it was impossible to manage him. He ate 10 or 15 slices of bread a day. Both eyes were operated on a year after I first saw him.

I have seen lipemia retinalis once in a boy who came in in mild coma. He had had diabetes probably not more than a month. Why he had such high blood cholesterol we do not know, but that is the reason we looked at the retina. We found a cholesterol of 870 mg. percent. One other interesting case was a child who noted that he could not see to the side as well as he thought he ought to. It was found that he had narrowed temporal fields of vision.

Pediatricians rarely see the serious conditions of which Dr. Krause spoke because, as a rule, the disease develops after the children have passed out of our hands. I can recall three cases that I saw after the war. Apparently, prior to 1941, retinitis proliferans was not recognized, or diabetics had not lived long enough to develop it.

One boy who was going into college had his eyes examined by a member of this society, and it was found that he had quite marked changes. In my crude ophthalmoscopic examination, I could not see anything but hemorrhage. He had a blood pressure of 190 mm. Hg and had albuminuria. The diabetes started at the age of two years and was discovered 17 years later.

Then there was a girl, aged 21 years, who developed retinitis about 15 years after the onset of diabetes. She is a patient of Dr. Steiner's and has been helped a great deal by one of the members of this society. The vision is still far from perfect.

A third patient was a girl whose diabetes started at the age of six and one-half years. When we saw her two years later, the condition was so severe that she required four doses of regular insulin a day. When we were able to give slow-acting insulin, she still required large doses. We transferred her to the adult clinic at the age of 16 years, and I heard nothing further from her until about 1947 when she called me and said "Doctor, I have a lovely little baby girl. Can't you do something for me; I am going blind."

Dr. Richard C. Gamble: I would like to mention briefly a rare and unfortunate oc-

currence in a juvenile diabetic. This youngster was watched from about the age of two years and, when she was at about the age of 18 years, I began to notice that the retinal veins were very dilated and, as you well know, that is what is seen before rubeosis of the iris takes place.

I did not know it at the time but she had not started to menstruate. As a rule an ophthalmologist does not go into that history, but sometimes it is advisable. Someone gave her stilbesterol to start menstruation and, shortly thereafter, she had massive hemorrhage of the vitreous, rubeosis of the iris developed, and secondary glaucoma.

She was sent to Baltimore to get some advice on whether X-ray treatment should be given for the rubeosis of the iris. They sent her back with a schedule of what should be done and we gave her the X-ray treatment.

The rubeosis entirely disappeared, the tension returned to normal, the eye is perfectly comfortable, but she developed a cataract, partly, I suppose, because of the X-ray therapy and partly because of the disease she already had.

It is advisable, therefore, in young diabetic girls, not to use stilbesterol.

Dr. Arlington C. Krause (closing): Dr. Newcomb's mention of the association of squint with diabetic mothers is interesting. That is an entirely new idea so far as I know. I would be interested in studying the fundi of these newborn children of diabetic mothers. I am interested also in premature infants of diabetic mothers. As you know, women who are diabetic tend to have trouble in producing live children; they may be stillborn or may be premature. We are, of course, very much interested in prematures of all sorts, as you know.

I would like to know whether Dr. Newcomb has seen diabetes in infants. There is no reason why a child should not be born with diabetes and I would be interested in the pediatrician's point of view as to what happens to the eyes in the early stages.

This problem is going to be more and more serious in the prevention of blindness. The number of diabetics appears to be increasing very rapidly, and we are going to have more diabetic people coming to us earlier in life and as they grow older, because the population as a whole is growing older.

GALACTOSEMIA AND GALACTOSURIA

DR. MATTHEW M. STEINER presented this paper which appears on page 841 of this issue.

Discussion. Dr. Richard C. Gamble: The occurrence of cataract in cases of galactosemia is one of the most interesting things to be encountered in pediatric ophthalmology. It would be of much greater importance if the disease occurred more often. The number of cases of galactosemia reported in the literature is very small, therefore few pediatricians have ever seen a case and I am sure that even fewer ophthalmologists have seen one.

In the cases reported before 1945 no mention is made of the presence of cataract, probably because no careful eye examination was made. In 1945, Bruck and Rapoport described the presence of cataracts and, in all the cases reported since, cataracts have been observed, so it is probable that they occur in all or nearly all cases.

In 1932, Kirby reported the effect of galactose on the lens, and, in 1939, Gifford and Bellows described the histologic changes in the lens produced by galactose. They noted that the opacity appeared earliest in the cortical fibers near the equator, the capsular epithelium showed change later, and the nucleus remained clear until very late. In other words the new rapidly growing fibers were affected first.

The point of greatest importance is that, both in experimental work on rats and in the clinical cases in babies, these cataracts are reversible if galactose is eliminated from the diet.

A case of galactosemia with cataract was

seen at Children's Memorial Hospital last year:

Michael M. was admitted to the hospital on January 25, 1951, at the age of seven weeks. He had been delivered by Caesarian section because his mother had toxemia. He did not gain weight, had an enlarged liver, and had albumin and sugar in the urine but no acetone. The sugar was nonfermentable. Milk was eliminated from the diet and replaced by Mull soy and Nutramigen.

The lens in each eye had a peculiar ring which appeared to surround the nucleus; it was more refractile than opaque, but could be seen both by external inspection with oblique illumination and with the ophthalmoscope. The lens opacity did not disappear as fast as had been hoped, possibly because the rigid diet was not adhered to as well as could be desired, but by February, 1952, the ring could just barely be made out.

Dr. David Shoch: The mechanism of both diabetic cataracts and galactose cataracts has been under investigation for many years and they present a most interesting phenomenon. We are apparently dealing with a quantitative disease. That is, the body can handle "normal" amounts of glucose or galactose and it is only when the concentration of these substances in the blood rises to great heights that cataracts develop. It is this point that I wish to make: that the cataract development is apparently dependent on the elevated blood sugar (galactose or glucose) rather than on the underlying disease *per se*.

How can we explain this phenomenon? Dr. Steiner mentioned interruption of the metabolic pathways and I should like to elaborate this point somewhat. It is our belief that we are dealing with a saturation of one of the enzyme systems concerned with the degradation of glucose and/or the conversion of galactose to glucose. Since the conversion of galactose to glucose is poorly understood, we have turned our attention to the degradation of glucose.

Glucose and galactose differ structurally only in the position of the hydroxyl group

on the fourth carbon atom, and the enzyme group known as aldolases operate to cleave the glucose molecule between the third and fourth carbon. We have, therefore, chosen to initiate our study by an investigation of these aldolases.

I might add that other sugars, such as xylose and d-arabinose which are very similar to glucose and galactose, except for the lack of one carbon in the chain, have also been reported to cause cataracts.

Dr. James E. Lebensohn: It is entirely unnecessary to postulate a toxic effect of galactose to account for the characteristic clouding of the lens. The high osmotic pressure induced by galactosemia, over 300 mg. per hundred cc., is sufficient cause. Initial dehydration of the lens is followed by subsequent precipitation of the soluble proteins. The nucleus is less affected because of its relatively small content of soluble protein.

Flocculation, which is reversible, occurs first; but if the galactosemia continues long enough, irreversible precipitation sets in.

The apparent cure after the galactose diet is stopped or the galactosemia is otherwise ameliorated is due to the new-growing healthy fibers which compress the opaque substance, so that eventually a thin perinuclear ring replaces the obvious cataract that was first visible.

Dr. Matthew M. Steiner (closing): I should like to thank Dr. Shoch, Dr. Gamble, and Dr. Lebensohn for their contributions to this paper. Dr. Shoch's discussion of chemistry is always very interesting. Probably some day we will find out what to do about substituting for the enzyme. Dr. Lebensohn's remarks made me think about some of the experiences we have had with these patients, and also those reported in the literature. Some of the cataracts have remained despite lowering of the galactose for some time, so that one feels that the cataract develops more on the basis of chronicity of galactosemia rather than on the extreme level of the galactose in the blood.

KIMMELSTIEL-WILSON SYNDROME

DR. HENRY T. RICKETTS: The reason, I am sure, why the Kimmelstiel-Wilson syndrome was selected for discussion this evening is because of its very close relationship to diabetic retinopathy, in which all of you are interested. I promised Dr. Puntenney that I would not encroach upon his field any more than necessary, so I shall not talk much about retinopathy but, if I mention it once or twice, I hope that he will forgive me.

The clinical picture of the Kimmelstiel-Wilson syndrome was described by these authors in 1936. It has become well-recognized by now, and consists simply of the appearance, in patients with long-standing diabetes, of albuminuria, edema, hypertension, retinopathy, and, often, a low serum protein. Its course is slow and rather insidious.

One sees in the diabetic clinic, patients who originally have no albuminuria and who, after some years, begin to show faint traces, then a little more, and, as the years go on, increasing amounts of protein in the urine. Gradually the other concomitants of the syndrome, the edema and the hypertension, appear, and about that time, or possibly before, evidences of retinal disease.

It has, compared to chronic glomerulonephritis of the ordinary variety, a rather benign and slow course and patients, instead of dying a few months after onset, may go on for a good many years.

The incidence of this syndrome depends upon what kind of population we are talking about, the quick or the dead. So far as examination of clinical patients is concerned, one finds this syndrome, at a stage when it can be confidently diagnosed, in about five percent of patients. In postmortem material, however, one can demonstrate lesions of the Kimmelstiel-Wilson type in approximately 20 percent of all patients dying with diabetes. So it depends upon the point of view.

It is obvious, I suppose, that it is easy to recognize it clinically once the disease has progressed far enough, and by the time it

has progressed far enough to recognize clinically, the pathologic lesions are well advanced.

It is twice as common in women as in men—an interesting fact—at least according to studies from the Mayo Clinic which appeared a couple of years ago in an excellent article by Henderson, Sprague, and Wagener in the *American Journal of Medicine* in 1947. This is a very good piece of work from a pathologic point of view. Previous papers have referred to the relation between retinopathy and the duration of diabetes.

One may, with equal validity, refer to the relation between the Kimmelstiel-Wilson syndrome (intercapillary glomerulosclerosis) and the duration of diabetes. If there is one thing upon which all are agreed, it is that the duration, more than any other single factor, predisposes to the development of this picture.

The question of whether this disease is related to severity of diabetes is much like the question concerning the retinopathy and the severity of diabetes. I would like to pause and go over with you for a moment the matter of how you tell whether a patient has severe diabetes or not. What are the criteria? It is not nearly as simple as one might think, and I can assure you, first of all, that it is not merely a matter of insulin dosage.

There are many patients who are quite sensitive to insulin, younger patients for the most part who, when insulin is removed, promptly go into acidosis. That may be true even though they take no more than 20 units of insulin per day—I am speaking of adults. On the other hand there are adult patients who require 80 or 90 or 100 or 150 units daily and who, when it is withdrawn, can go on indefinitely without any ketosis at all.

Which patient has the more severe diabetes? I submit, the one who goes into acidosis.

It must be realized that the people who write and talk about these subjects have a difficult problem. How are they going to characterize severity of diabetes? If they

say it is 1+ severe, or 2+ severe, they can be challenged—what do you mean by 1+? They have to fall back on insulin requirement.

I do not blame them, we all do it. I just want to warn you that insulin requirement is not a complete criterion for the severity of diabetes. So when we try to correlate the incidence either of retinopathy or Kimmelstiel-Wilson disease with the severity of diabetes, we have to watch our step.

With those reservations, and taking into account these difficulties I have spoken of, I will turn around and say that I think Kimmelstiel-Wilson's disease is more common, at least during life, in patients with severe, prolonged diabetes than it is in patients with mild diabetes or diabetes of short duration. Again, it depends upon whether one is speaking from the standpoint of the autopsy room or the clinic. The average age at death of patients dying with the Kimmelstiel-Wilson syndrome is 58 years. On the other hand, the average age of patients presenting themselves to the clinic and exhibiting this syndrome is considerably under 40 years.

What is the relationship between the incidence of intercapillary glomerulosclerosis and control of diabetes? Again I must refer to the analogy between this condition and retinopathy. How do you define control? It is not easy, any more than severity is easy to define.

You may see a patient once a week or once a month in your office, and take a blood sugar and have him bring a 24-hour specimen of urine which shows a certain amount of glucose. If the glucose in the urine is as much as 10 gm. a day, let us say, and the blood sugar is around 120 mg. percent, you say this patient is reasonably well controlled. He comes back in a month and you find things approximately the same and you feel that he is still in pretty good control.

But do you know what has been happening to him the other 29 days? You do not.

He may furnish a record of his tests and that may be valid in some cases but I think

it would be quite invalid in others.

What criterion are you going to set up for how well a given patient is controlled? And over how long a time?

One must not forget that the blood sugar represents a single incident in a long diabetic life and that what counts in this business, if anything counts, is the day-to-day customary degree of control. So that we do not know what we are talking about, most of us, when we say our patients are well controlled or poorly controlled. We have ideas, we have suspicions, but to have incontrovertible proof is a very different matter.

Dr. Krause referred to the difficulty with which some of the younger patients are controlled and so did Dr. Newcomb. If you take the position that good control of diabetes prevents renal lesions as well as retinal, and then turn to the young patients about whom we are most concerned, you are discouraged and surprised to find how poor the control is in those patients despite the very best you can do.

The instability of the young diabetic patient is a very vexing thing and, although one may believe that good control delays or minimizes or prevents these lesions, nevertheless to achieve that good control in young patients is no easy matter.

The fact that young people so commonly develop Kimmelstiel-Wilson's disease and retinopathy provides a poor basis for saying either that good control would prevent it or would not prevent it, because most of these youngsters are rarely very well controlled a large part of the time.

These are really tangential considerations to which I think it is important to call attention. I shall return to the topic at hand, the Kimmelstiel-Wilson syndrome.

(Slide.) This is a renal glomerulus and one sees here the typical spheroid globular bodies scattered throughout, to which Kimmelstiel and Wilson first called attention a number of years ago. Often this occurs with thickening of the afferent or efferent glomerular arter-

ioles, but it occurs by no means always.

It is a lesion which is seen in a great many diabetics but not exclusively in diabetes, because approximately 10 percent of patients dying with chronic glomerulonephritis also exhibit lesions which are to all intents and purposes indistinguishable from this one.

The composition of these globular bodies has been a matter of considerable interest. They were at first thought to be hyaline but that did not hold up; amyloid, it certainly is not.

The most recent work appearing from the laboratory of McManus indicates that this is one of the mucopolysaccharides. It takes the periodic-acid stain, with which you are familiar from the work of Friedenwald who employed this stain for bringing out the capillary aneurysms in flat preparations of the retina. It is the stain that picks out carbohydrate in tissues and these globules take that stain rather well.

If the globules contain mucopolysaccharides, it raises the question of whether the traversing of the glomerulus by a plasma highly concentrated with respect to glucose may have a causal relationship to the development of these bodies. That is entirely speculative at present; one can only raise the question.

The Mayo Clinic investigators found that, in patients who showed this lesion to a marked degree, the diabetes has been in existence for an average of 11 years; with mild lesions the diabetes has been in existence for only eight years and, finally, diabetic patients who showed no such lesions had had the disease for only five years. So here is pathological evidence that duration has something to do with the appearance of lesions.

Of the autopsied patients studied by the Mayo group, 60 percent with intercapillary glomerulosclerosis had had hypertension during life, 50 percent had poor pedal pulses, 12 percent had gangrene, 23 percent had neuritis of the typical diabetic variety, and 69 percent had retinopathy. Thus the close association of this lesion with other vascular

lesions in diabetes is well brought out. The part of the vascular bed with which this has the closest affinity is the capillary system of the retina, and of course it is fascinating to speculate on what there may be in common between the renal glomerulus, the retinal capillaries, and the capillaries of the skin exhibiting increased fragility which predisposes all of them to injury in diabetes.

We speak of cause—we really do not know anything about it. We do not know whether it is the excessive amount of glucose passing through the kidneys which damages the vessels, or whether it is hyperlipemia, which occasionally is present in these cases but by no means always. In fact I think it is uncommon for hyperlipemia to be present in a well-treated diabetic for any length of time.

We have really not the foggiest idea of the pathogenesis of the lesions. Can they be prevented? Again, like the eye story, that is open to question. I think the best answer to this, and I am going to use an eye slide, if I may, has come from a recent study.

(Slide.) The Joslin group not long ago recalled 200 odd patients with diabetes, beginning in childhood, which had been up to 20 years or more in duration. Out of this collection of diabetic patients, the retina was examined thoroughly in 103 patients, all of whom had had the disease for 20 years or more.

Doing the best they could, despite the difficulties we have mentioned, to assign a level of control to these patients, they classed them as having had excellent, good, fair, and poor control. Control in the last group really was poor, there is no question about that; the excellent ones were probably pretty good; the intermediate ones, I think, there is some question about. The degree of retinopathy was classed as none, minimal, moderate, and marked.

Confining ourselves to the groups of excellent control and poor control, one can say that of the four patients with excellent control none had moderate or marked retinopathy, three had none, and one had mini-

mal. There are a total of 58 patients with poor control and 40 of them had moderate or marked retinopathy, six minimal, and 12 none.

I think this is very instructive. It tells us that, although 12 patients went for 20 years with poorly controlled diabetes, they did not develop retinopathy. On the other hand, it tells us that the majority of patients who were poorly controlled for long periods of time did develop retinopathy to a rather marked degree.

The same thing can be said about the kidneys; I do not have the figures but they are roughly similar. One has to say, then, that control of diabetes is not the whole story in preventing these lesions either in the kidney or in the eye, but that it probably does minimize the lesions in severity and delays the time of their appearance. So when you send your eye patients to the internist for the better control of diabetes and the prevention of the disease process in the eye, you are entitled to reassure the patient to some extent—but please don't overdo it.

Discussion. Dr. Irving Puntenney: Certain problems related to this subject are far from solution. So far as the ophthalmologist is concerned the following questions need to be answered:

1. Can the ophthalmologist help in the recognition of the condition during life?
2. What are the changes in the ocular fundi?
3. What is the incidence of intercapillary glomerulosclerosis in patients examined by the ophthalmologist?

Kimmelstiel and Porter have shown that there are no definite clinical features to establish the diagnosis of intercapillary glomerulosclerosis. The only sure diagnosis is a pathologic diagnosis. One can say, however, that in a patient, 50 or more years of age, with chronic diabetes, nephrotic edema, and albumin in the urine, with a high blood cholesterol, a diagnosis of intercapillary glomerulosclerosis can be made with almost 100-per-

cent accuracy. Such a diagnosis is of importance because it carries a grave prognosis, especially since the condition cannot be influenced by the treatment of diabetes.

The ophthalmologist can help in the diagnosis of this condition, but only by his appraisal of the eyegrounds. Practically speaking, this means that the presence of retinopathy in a diabetic can be of value in making the diagnosis of intercapillary glomerulosclerosis, if not clinically, at least percentage-wise.

Henderson, Sprague, and Wagener, in their report from the Mayo Clinic, found the incidence in diabetics to be 27.1 percent in women and 15.5 percent in men. On an average, this means that one diabetic out of every five has intercapillary glomerulosclerosis. In connection with these figures, it is interesting to note that Wagener found the incidence of retinopathy in proven cases (by proven I mean necropsy cases) to be three times as great as in the cases of diabetics without intercapillary glomerulosclerosis.

These percentages can be appreciated if diabetic retinopathy is broken down into four groups and the incidence of intercapillary glomerulosclerosis determined in each group. The groups are those seen in diabetes:

1. Hemorrhages (including microaneurysms)
2. Hemorrhages and punctate exudates
3. Hemorrhages and punctate exudates and cottonwool exudates
4. Venous disease with proliferating retinopathy

At autopsy, 36 percent of all the diabetics had retinopathy. The average age of the group was 60 years. By analyzing Wagner's statistics on those with retinopathy the following interesting figures have been obtained: 35 percent of all cases with retinopathy fell into Group I, and of this number 21 percent had intercapillary glomerulosclerosis and 79 percent did not. Of the 27.5 percent of cases classified as Group II, 73 percent had intercapillary glomerulosclerosis and 27 per-

cent did not. There were 22.5 percent of the total cases with retinopathy in Group III, and of this number 88 percent had intercapillary glomerulosclerosis and 12 percent did not; five percent of all the cases had proliferative retinopathy and venous disease and all of these had intercapillary glomerulosclerosis.

These figures are of practical importance percentage-wise. If a diabetic has retinopathy, then approximately one out of five in Group I has intercapillary glomerulosclerosis; three out of four in Group II have intercapillary glomerulosclerosis; nine out of 10 in Group III have intercapillary glomerulosclerosis; and all those with venous disease and proliferative retinopathy are affected.

Dr. Henry T. Ricketts (closing): This is a very ingenious calculation Dr. Puntenney has done, and I have no doubt of its validity. One can go a little further and say that from the other point of view all patients who have proven intercapillary glomerulosclerosis have retinopathy. I think that is almost without exception; it is a very high incidence.

One other point I should like to make. A curious thing has been noted recently, namely, that many patients with intercapillary glomerulosclerosis, as they go on in their diabetic careers, show marked amelioration of their diabetes.

This has been brought out in two publications from Johns Hopkins Hospital, one appearing in their *Bulletin* and the other in the *New England Journal of Medicine*. Some very startling things have been claimed by the authors, and I think some of them, at least, are true.

In one patient with the Kimmelstiel-Wilson syndrome who had had diabetes for 12 years, requiring 50 units of insulin a day, they took away all insulin and he did not go into acidosis but went merrily on for a long period of time.

They have reported a good many cases showing this marked diminution of insulin requirement in the presence of long-standing Kimmelstiel-Wilson's disease. I do not

know what it means, but it is something very interesting and worth following.

Richard C. Gamble,
Recording Secretary.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

March 3, 1952

DR. ADOLPH POSNER, *president*

DIFFERENTIAL DIAGNOSIS OF PERI-OCULAR SKIN DISEASES

DR. FREDERICK REISS presented a paper on this subject during the instruction period.

BILATERAL SQUINT SURGERY: A PRELIMINARY REPORT

DR. FRANK D. COSTENBADER said that he had operated on a series of 289 cases of comitant strabismus. An analysis of post-operative comitance and incomitance was made. "Incomitance" was arbitrarily defined as "a difference in ocular alignment of more than 10 prism diopters in the measurements in the two temporal horizontal fields of gaze."

Following unilateral surgery (159 cases), 77 percent were immediately incomitant and 64 percent were finally incomitant.

When unilateral surgery was later followed by similar surgery on the corresponding muscle of the other eye (39 cases), only 23 percent were finally incomitant.

When simultaneous bilateral symmetrical surgery was done (89 cases), 15 percent were incomitant immediately, while only five percent were incomitant at the last measurement.

Of the unilateral cases, when proportionate amounts of recession and resection were done (42 cases) as opposed to disproportionate amounts of such surgery (134 cases), about equal percentages of incomitance resulted (60 percent as opposed to 54 percent) in each group.

Assuming that the goal in the treatment of strabismus is (1) Straight eyes, (2)

comitance, and (3) fusion, the association of straight eyes and fusion with comitance and incomitance was investigated. It was found that a somewhat higher percentage of comitant cases was associated with final straight eyes and fusion than was true for the incomitant cases.

It was concluded that bilateral simultaneous symmetrical surgery for strabismus results in a high percentage of postoperative comitance, and, therefore, in a greater percentage of cures.

Discussion. Dr. Aebli said that he agrees in general with the principles laid down by Dr. Costenbader; that he likes to spread out the upper operations over several muscles, instead of doing one muscle in one eye, in order to get better conjugate gaze—right or left. He agreed that congenital defects give poor results, compared to those that are acquired. Patients with the accommodative type of squint that develops at the age of 18 months or so, usually do well with a full correction, or bifocals, and many of them do not require surgery.

Dr. Gailey agreed thoroughly with the principles laid down by Dr. Costenbader.

Dr. Brown agreed in general with the principles of spreading out the operation over several muscles. He stressed that, in the congenital paralyses, there is very little secondary contracture in the field opposite to that of the paralyzed muscle; hence, there is good binocular vision here. With surgery, one can shift the field of binocular vision but one cannot enlarge the field of binocular vision.

Dr. Smith agreed with Dr. Costenbader and mentioned the importance of these principles in obtaining binocular single vision. He asked Dr. Costenbader what he thought was the best age range for good muscle surgery.

Dr. Meek said that he had used principles similar to those of Dr. Costenbader for a long time because the subsequent position of the globe was better; that is, the palpebral fissure remained more normal when the operation was divided between two muscles in

an eye rather than being done on one only.

Dr. Kestenbaum said that Dr. Costenbader's method anticipates the next step in the development of treatment for strabismus. At the present, we are still in the stage of searching for a method to guarantee parallel position of the eyes in the primary position. If this aim is achieved, the next step will be to achieve parallel position of the eyes in lateral gaze. Therefore, Dr. Costenbader's conception of symmetric surgery as a means to reach comitant eye movements looks to the future.

Dr. Schlossman wanted to know if Dr. Costenbader differentiated between alternating and monocular squints, as to his types of surgery.

Dr. Costenbader replied to Dr. Schlossman that he did not differentiate between them. He thought that whether the squint was monocular or alternating was a matter of chance and should not influence the type of surgery. To Dr. Smith he replied that he likes to see the patient at least three times to make sure that the deficit is of a constant nature. He does not fix a definite age for operation but thinks that the earlier the surgery, the more conducive to binocular single vision. He was enthusiastic about Dr. Meek's remarks about the better symmetrical appearance of the eyes with spreading out of the muscle surgery, especially in the same eye. Dr. Costenbader mentioned that in doing binocular surgery, he takes the bandages off in 24 hours, in order to make the patient happy.

IMPRESSIONS FROM 45 YEARS OF CATARACT SURGERY

DR. WATSON GAILEY of Bloomington, Illinois, mentioned the great advantages accompanying practice in a big city rather than in a so-called rural location. He described the flash and brilliance of some ophthalmic surgeons but admired the careful calculating type. He spoke of Schoenberg stressing the importance of the emotions as an etiologic factor in glaucoma and paid tribute to Arnold Knapp, John Wheeler, and other New York

ophthalmologists of note and said that he envied men who enjoyed the benefits of associating and conferring with them in a professional way.

He questioned the sense of prolonged and expensive hunts for foci of infection. He stressed the importance of the relationship between patients and surgeons, advised against a professorish or "high hat" attitude, and felt that the patient should feel that his doctor is a real friend.

During the preparation of the patient and following surgery, there should be no unnecessary talking in the operating room. In his opinion, operating in the sitting position was conducive to a much better technique.

The speaker felt that the various treatments advised for epithelial invasion of the anterior chamber were useless and the hope for a cure lies in prevention.

Preparation of the field of operation, in his opinion, was largely a pose and prolonged flushing of the eye might possibly be a mistake.

Retention of the zonular-capsular barrier adds to the integrity of the anterior segment. He felt that the hard-working patient would have a stronger, better eye if his mature cataract were removed by the combined extracapsular method.

Among other things Dr. Gailey discussed the great value of Hydase in the prevention of vitreous loss. Hydase produces a soft eye but a safe one. In his practice, he seldom saw a bead of vitreous and questioned whether vitreous ever exists in this small quantity.

There are a great number of younger men who have been advanced into excellent surgeons by being taught the keratome section with scissor enlargement. He spoke of the importance of rubber gloves and the fallacy in contending that they interfere with the operator's sense of touch.

Anesthesia should be perfect—local and not "vocal." Akinesia must be flawless. If there is question as to whether canthotomy should be employed in a given case, resort to this procedure. After retrobulbar injection is

made, the section should not be attempted until free movement of the eye can be made in all directions with fixation forceps.

Dr. Gailey felt that the round pupil was overrated, that the simple extraction was more hazardous because of the incidence of postoperative iris prolapse, and that the great majority of patients are very little concerned as to the shape of the pupil but are deeply concerned with an uncomplicated successful sight-producing operation.

He feels that cataracts should be delivered slowly, principally by pressure, and that the erisophake or capsule forcep should be used simply as a guide. Above all, the surgeon's instruments must be good.

Discussion. Dr. Meek stressed that he was told by Dr. Chandler that pressure was put on the eyeball for five minutes before operating it, to soften it. He wanted to know how Dr. Gailey felt about it.

Dr. Minsky was enthusiastic about Dr. Gailey's stressing the extracapsular operation, and urged that the younger men pay more attention to extracapsular operations.

Dr. Payne mentioned some of the remarkable achievements of Dr. Gailey, especially his participation in some of the work of the past war.

Dr. Rolett asked Dr. Gailey what percentage of epithelial downgrowths he had encountered.

Dr. Gailey said to Dr. Meek that he thought that Dr. Chandler's method of pressure was very smart. As a matter of fact, before the days of Hydase, if the anterior chamber was lost immediately after section, he would allow the patient to close his eye, and then make slight pressure for about five minutes through a wet pad over the closed eye, and he believes that he avoided a good deal of vitreous loss by doing this. He believes that the choroidal bed is thus allowed to re-adjust itself to the change in pressure made by the section. He quoted the late John Wheeler on the importance of making a simple procedure suffice, when necessary, instead of complicated procedures.

Bernard Kronenberg,
Recording Secretary.

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THE NEED FOR REVISION OF UNDERGRADUATE TEACHING IN OPHTHALMOLOGY

The great emphasis on the importance of the general practitioner in the field of medicine by the American Medical Association in recent years has resulted in some interesting changes in the outlook of the general practitioner and the medical student toward specialization.

This new attitude toward general practice

has resulted, in some instances, in the acquiring of a false sense of ability to care for some of the complicated conditions encountered in ophthalmology. This self-assurance has been furthered by the development of the antibiotics, cortisone, and ACTH, and by the literature sent out by the manufacturers.

This has resulted in the improper treat-

ment of some cases until the damage has progressed to the irreversible stage. An example of this is a case of bilateral congenital glaucoma treated by the instillation of cortisone for five months before the parents of the patient finally insisted on an opinion by an ophthalmologist. Another instance was a case of iritis in which penicillin ointment was employed for three weeks with the resultant development of secondary glaucoma and a penicillin reaction.

The trend to discredit specialization is also reflected in the change of attitude of medical students. In one school, the senior class is quite outspoken in its opinion that the school spends too much time on specialties and does not emphasize the medicine of general practice. The students have a tendency to "cut" the specialties both in the classroom and the clinic unless they feel that the teaching is such that it is of importance to general practice.

This attitude is further reflected in the applications for internships. In one university hospital that has six-month services only two students applied for internships, the remainder of the class applying to hospitals where the internships are rotating. It was interesting that in discussing the matter with the present senior class it was found that over 45 per cent of the class was planning on going into general practice. This same tendency has been observed in a number of medical schools.

Probably primarily as the result of the war and the increase of the average age of medical students of the past few years, the students are better organized and do not hesitate to express their opinion of an instructor or his course. In some instances, a class representative calls on the instructor with the class's criticism. A further evidence of this tendency is the recent attempt of a group of interns to go on strike with the hope of making it a national affair. They even solicited moral and financial support from interns all over the country.

It is this new independence of thought, together with the frank, honest, constructive criticism that has been responsible for calling to our attention the need for a change in the undergraduate teaching in ophthalmology.

How does this modern trend affect the teaching program in undergraduate ophthalmology? With the gradual decrease of hours of teaching allotted to the specialties, it is quite obviously impossible to make specialists out of the students. We do, however, have a grave responsibility in seeing to it that the student is taught the essentials that are required of him to meet the present situation.

What, then, should the medical student be taught about ophthalmology? He should be taught to diagnose and care for properly the conditions that at present are considered to be within the province of the general practitioner. He should have a thorough understanding of the differential diagnosis of the red eye and the danger of the improper use of mydriatics or miotics. He should have a general conception of glaucoma and its dangers. He should be told that the old tradition of the general practitioner of instilling atropine into every red eye is not only unnecessary but that at times it may be dangerous. He should be familiar with the proper removal of a foreign body of the cornea and its after-care, together with the dangers of neglect.

He should be taught the emergency treatment of eye injuries with particular emphasis on the dangers of doing too much, together with the importance of the proper first aid in the preservation of the patient's vision.

The treatment of some of the simple external diseases such as the hordeolum, chalazion, and blepharitis should be understood. The proper use of and the dangers of the antibiotics used topically should be stressed, and the student should be informed that there are other therapeutic agents that have stood the test of time.

The proper use of the ophthalmoscope and

the importance of the fundus lesions in the evaluation of general diseases bear emphasis. In the discussion of medical ophthalmology the ophthalmology of pediatrics should not be neglected.

The student should also be told of the legal responsibility he assumes when he treats an eye. This discussion should include such items as the legal responsibility of X-ray examination in cases of trauma of an eye where metal has struck metal.

It would appear that there is no place in the curriculum for teaching ophthalmic surgery aside from a simple explanation of what is done in the surgery of congenital and senile cataracts, glaucoma, and muscle surgery. In discussing muscle anomalies, only the very basic conditions need be mentioned without going into the intricate details of these anomalies. In refraction, only the simple definitions of the various types of refractive errors together with the symptoms they produce need be considered, entirely avoiding the confusion caused by the necessarily inadequate discussion of optics.

It was most interesting in reviewing Adler's new edition of Gifford's textbook recently to find that he has similar convictions and that he has omitted the details of surgery, muscle anomalies, and the more technical phases of ophthalmology and has placed greater emphasis on the broader scope of our specialty.

It has been the changed medical student of today who has called to our attention the necessity for revision of the undergraduate teaching of ophthalmology. We have the grave responsibility of teaching the medical student the ophthalmology that is needed to meet the present-day requirements of the general practitioner. It is equally important that he also be taught his limitations. It is only by doing this that we can hope to reduce to a minimum the unnecessary loss of vision. That teachers of ophthalmology are aware of this is evidenced by the teachers' section of the American Academy of Ophthalmology

and Otolaryngology where the entire problem is receiving serious consideration.

Frederick C. Cordes.

WILLS EYE HOSPITAL

FIFTH ANNUAL CLINICAL CONFERENCE

The fifth annual clinical conference of the staff and ex-residents of the Wills Eye Hospital, Philadelphia, was held at the hospital on March 20 and 21, 1953. Registration approximated 350.

The meeting was opened by Dr. Ivan J. Koenig with a clinicopathologic case report of a malignant melanoma of the iris in a one-eyed patient, observed for 20 years.

Dr. Clyde H. Jacobs presented a movie showing several cataract extractions under intravenous pentothal-sodium anesthesia.

The hospital's research staff, under the direction of Dr. Irving H. Leopold, made the following reports on five of their current projects:

Dr. Virginia L. Weimer, Dr. Harry Green, and Dr. Irving H. Leopold described a method for determining steroid concentration in the intraocular fluids which has enabled them to establish the presence of certain steroids in these fluids of the experimental animal eye.

Dr. J. Eisenberg, Dr. Irving H. Leopold, and Dr. J. W. Hallett presented evidence showing that the radioactive isotope P^{32} could be helpful in the differential diagnosis of intraocular tumors. The ability of the normal eye to concentrate P^{32} was determined and the percent variation of over 50 normal eyes was used for this determination. More than 40 eyes suspected of having intraocular neoplasms were then subjected to this test. Wherever the probe could reach the suspected area, positive readings were obtained in histologically confirmed cases of intraocular neoplasms. Those neoplasms, which were in the extreme posterior segment of the globe where it was difficult for the probe

to reach, occasionally produced negative results. All cases of serous detachment gave negative results. Five inflammatory conditions gave positive uptake values. The authors tentatively concluded that this is a valuable method to help in the differential diagnosis. They offered it simply as an adjunct and not to be used to supplant any technique already available.

Dr. William F. Kratka and Dr. Irving H. Leopold arrived at the following tentative conclusions from their studies with isonicotinic acid hydrazides in experimental and clinical ocular tuberculosis:

Isonicotinic hydrazides will control experimental and clinical ocular tuberculosis when therapy is maintained for a long period of time. In the experimental animal, improvement was not noted until after 50 days of therapy, when treatment was instituted nine days after inoculation into the anterior chamber or cornea.

If therapy was stopped too soon, even though there was obvious clinical improvement, recurrences developed. The best results were obtained in those in whom therapy was continued for six months. Evidence of clinical quiescence of the lesion often belies the true picture, in that histologic preparations of the same eyes show definite activity which may account for the numerous recurrences with too short a period of therapy.

Therapy of experimental lesions compared favorably with streptomycin, para-aminosalicylic acid. In some instances, superior results were obtained with the combination of the three drugs than with streptomycin and para-aminosalicylic acid alone. In some, isonicotinic acid was superior in the results in the experimental eye to that obtained by streptomycin and para-aminosalicylic acid.

Penetration studies were also done following the subconjunctival intramuscular topical administration of isonicotinic hydrazides. By all forms of administration, adequate penetration into the intraocular tissues and fluids could be obtained.

Dr. J. O'Rourke and Dr. Irving H. Leopold reported the inability of the enzymes, streptodornase and streptokinase, to lyse rabbit blood, and further demonstrated the necessity of a human serum factor, namely, plasminogen for the lysis of human and experimental animal blood by these enzymes. Their studies indicated a safe dosage of these enzyme preparations for intradermal injection. It was shown that many of the toxic features of the commercially available enzyme, streptokinase, are due to the contained hyaluronidase. The action of these fibrolytic enzymes is greatly influenced by temperature changes, more so than by concentration.

The length of time that the enzyme remains in the anterior chamber is of practical importance. In trials against standard experimentally induced anterior-chamber hemorrhages, the combination of the injection of the enzymes plus paracentesis and flushing of the anterior chamber gave the most satisfactory results. In low concentrations, these enzymes lose their anticoagulant properties. Apparently this property may be due to impurities. These enzymes were found to have the ability of provoking antibiotic response.

Dr. Adolph W. Vogel and Dr. Irving H. Leopold described a method for producing experimental posterior-segment lesions. They demonstrated the production of localized inflammatory and neoplastic lesions in the choroid with their technique.

Dr. Warren S. Reese and Dr. Turgut Hamdi reported their experiences with the Ridley implant in cataract surgery. Dr. Reese has performed 14 of these operations at the hospital during the past year, with favorable results in 12 of them.

Dr. P. Robb McDonald spoke on the indications for scleral resection in retinal separation as a primary procedure rather than as a "last resort" procedure in cases which have a poor prognosis.

Dr. Wilfred E. Fry, Dr. Max Kasser, and Dr. Samuel DeLong advocated excising a partial thickness of the sclera as a valuable

addition to the surgical treatment in retinal detachment. Their conclusions were based on experimental work on rabbits' eyes.

Dr. Robert E. Shoemaker discussed the ocular complications of erythema multiforme exudativum. He described an unusual case of an eight-year-old boy who presented symptoms of an eruptive fever, stomatitis, endophthalmitis with vision reduced to light perception, and arthritis with effusion. This, he considered a probable variant of erythema multiforme. With the use of systemic cortone all symptoms disappeared within a week with the exception of those of the eyes. Vision eventually recovered to 20/30 three months following the onset.

Dr. Raynold N. Berke accompanied his splendid movie on resection of the levator palpebrae muscle for blepharoptosis with many practical and instructive comments.

In general terms and based on more than 800 cases over a three-year period, Dr. Edmund B. Spaeth gave the indications and basic principles for surgery of the vertically acting muscles in strabismus.

The Arthur J. Bedell Lecture was given by Dr. Ellen F. Regan in the absence of Dr. John H. Dunnington. The paper was entitled: "Absorbable sutures in cataract surgery," and was of joint authorship by Dr. Dunnington and Dr. Regan.

Their conclusions were based on experimental studies and clinical observations. They found that the initial response with catgut sutures was a polymorphonuclear reaction which with the plain type was rapid and marked, leading to an early disintegration of the suture. When mildly chromicized material was used, this polymorphonuclear response was less pronounced and the suture remained intact for about seven days. Fibroblastic proliferation became evident on about the fifth day, as did increased vascularization of the wound.

During the second week, the healing process progressed and, at the end of 14 days, the wounds appeared well healed but somewhat broader and more vascularized than

comparable ones closed with silk. The increased vascularization of these wounds is an undesirable feature but this is counterbalanced by the relative absence of tissue necrosis and of epithelial invasion that the authors have found in the presence of silk sutures.

In view of these findings and their present clinical experience, the authors felt that mildly chromicized catgut is a satisfactory material for closing cataract incisions.

An important "repeat" feature of the conference was the color television program presented by the members of the surgical staff of the hospital, through the courtesy of Smith, Kline, and French Laboratories. These surgeons are becoming expert T-V operators as well as commentators.

Fourteen commercial exhibitors were also on hand with splendid displays.

As in former years, the meeting was not without its social side. The first evening, there was an informal reception for the doctors and their wives at the Barclay Hotel, followed by a delicious dinner. The Wills Eye Hospital Society held its annual dinner at the Union League Club on Saturday evening.

Kenneth L. Roper.

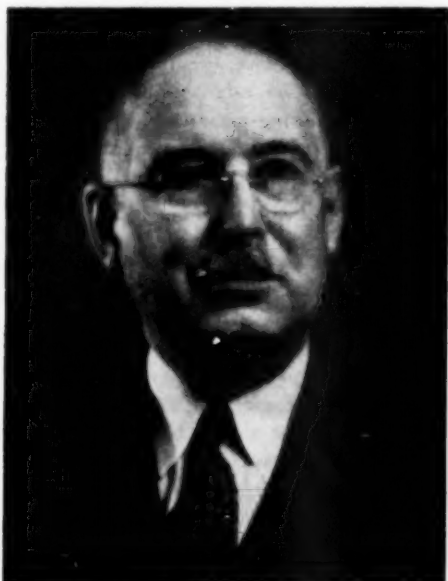
OBITUARY

EDWARD VAIL LAPHAM BROWN
(1876-1953)

Another major contributor to the credit side of modern American Ophthalmology is gone: Edward Vail Lapham Brown, or "E. V. L." as most of his colleagues spoke of him, was called from this world, from his family, and from a still very active professional life on March 1, 1953.

As successful organizer of systematic, carefully graduated postgraduate education in ophthalmology, Dr. Brown was known personally to a good section of today's practicing ophthalmologists. To his many direct and indirect pupils the loss of their oph-

thalmologic father and counselor will be mitigated by the lastingness of the foundation he laid for them in terms of ophthalmologic concepts, practices, and professional honesty. For those who did not know him a brief description of the man and his work is



EDWARD VAIL LAPHAM BROWN

herewith attempted aiming at the conciseness and accuracy characteristic of the deceased.

Born in Morrison, Illinois, Edward Brown sought and received a very broad medical education in Chicago, taking up ophthalmology as a specialty soon after his graduation from Rush Medical College. At the Illinois Charitable Eye and Ear Infirmary—one of the institutions indebted to Brown for a permanent elevation of its scientific status—he came under the influence of Ferdinand Carl Hotz, the German-born physician and pupil of Helmholtz and Graefe who had brought the benefits of almost the broadest possible scientific horizon into ophthalmology. To some extent it was Hotz's influence that induced Brown, already a licensed physician practicing ophthalmology, to take further scientific collegiate work which

earned him the degree of bachelor of science from the University of Chicago in 1902.

Early in his professional career he established personal contacts with several of the European schools. He was particularly attracted by the Viennese group, its master Ernst Fuchs and his associates, Salzmann, Meller and Lindner. It has been said that E. V. L. Brown's ophthalmologic thinking was more European or Austrian than American. To me, Dr. Brown was fundamentally a seeker of breadth in medical thinking, a synthetist of findings and views if they stood up under his ultrafair but nevertheless critical analysis.

The Viennese school undoubtedly impressed him deeply and, for a long time, held a central position in his ophthalmologic horizon. This manifested itself in Brown's early publications dealing with the pathohistology of uveitis, his translation of Salzmann's *Histology of the Human Eye* (The University of Chicago Press, 1912), and, some years later, of Fuchs's *Textbook of Ophthalmology*. But the second decade of this century found him busily engaged in a typically American field of study—the concept of focal infection applied to ophthalmology.

Setting a lasting example of mutually fruitful coöperation between ophthalmologist and internist, E. V. L. Brown and Ernest E. Irons made systematic clinical studies of the incidence of foci of infection in cases of uveitis, of the relationship between the activity of these foci and the activity of the uveitis, and of the effect of eradication of these foci upon the course of the uveitis. Continued for over 15 years with the greatest possible objectivity and accuracy of observation these studies became a classic in the field of uveitis, establishing a standard for all subsequent investigations into the etiology of uveitis.

One other field of special interest to E. V. L. Brown was the application of statistical methods to the refractive state of the human eye and the variations of this state

during life. An ardent advocate of the most complete cycloplegic as a means of arriving at basic refractive measurements he had in his office and university records an inexhaustible source of reliable data concerning refractive changes in the same individual. These data were the basis of several important publications.

In recognition of his devotion to ophthalmology as an academic discipline and of his extraordinary ability as an administrator and teacher, Dr. Brown was offered more headships of departments and occupied such positions for longer than most academicians of his generation.

From Rush he moved to Illinois in 1917 and from there to Chicago in 1926. When the statutes of the University of Chicago forced him to retire from the headship of a department that he had built up "from scratch" and guided to national prominence during 16 years of tenure, his friends at the Presbyterian Hospital prevailed upon him to accept the chairmanship of their Department of Ophthalmology, thus extending by another five years Brown's already very long academic life. Throughout his life Brown managed, by means of a very strict schedule, to divide his long working hours equally between private practice and academic work.

Dr. Brown's favorite ophthalmologic society was the American Ophthalmological Society of which he became a member in 1908, president in 1940, and recipient of the highest award, The Howe Medal, in 1942. Aside from the directly ophthalmologic approach to blindness he very generously lent his services to organizations for the prevention of blindness or betterment of the status of the blind. For 33 years he was a devoted member of the Board of Directors of the Illinois Society for the Prevention of Blindness. In that capacity he worked tirelessly not only toward making all prevention programs of the society more effective, but also toward raising the necessary funds. In recognition of his work on behalf of the blind, The St. Louis Society for the Blind

awarded him the Leslie Dana Gold Medal in 1951.

During the latter years of his life, E. V. L. Brown added to his many self-imposed duties the betterment of the social, professional, and scientific status of the Negro medical student and the Negro physician. His appointments to the chairmanship of the Chicago Committee on Human Relations and to the presidency of the Board of Trustees of Provident Hospital in Chicago were indicative of his feelings and aims in these matters.

Again by adhering to a very strict schedule, he had time for his family and his friends. His principal recreations were reading of contemporary literature and travel, his favorite sport tennis. He is survived by his wife, the former Frieda Muench Kirchoff who, by her many social gifts and by the profound understanding of what he and ophthalmology meant to each other, contributed immeasurably to his professional success. Among the four living children is one ophthalmologist, David Lapham Brown.

As the confirmed optimist that he described himself to be, he led a happy life, despite a number of illnesses, the tragic loss of one son, and the unavoidable reverses incurred in the practice of ophthalmology and in human relationships. In absolute measures, however, the happiness that life gave him could only have been a small fraction of the happiness he gave to thousands and thousands of others.

Peter C. Kronfeld.

XVII INTERNATIONAL CONGRESS OF OPHTHALMOLOGY

The XVII International Congress of Ophthalmology will take place at the Waldorf-Astoria Hotel in New York City, September 12 to 17, 1954.

The American Express Company has been appointed official travel agent for the congress and will offer assistance in obtaining travel accommodations. In order to provide the greatest possible assistance in obtaining

hotel accommodations a special housing bureau has been established. Arrangements have also been made for low-cost accommodations in the residence halls of Columbia University.

William L. Benedict, M.D.
Secretary General
100 First Avenue Building
Rochester, Minnesota

BOOK REVIEWS

INTRODUCTION TO PHYSIOLOGIC OPTICS. By Armin von Tschermak-Seysenegg. Translated from the second German edition by Paul Boeder, Ph.D., Springfield, Illinois, Charles C Thomas, 1952. 305 pages, 151 illustrations, author and subject indices. Price: \$10.50.

A deepening interest in visual physiology prompted the late Walter B. Lancaster to encourage and promote publications in this field. He wrote the foreword to Ogle's *Researches in Binocular Vision* and likewise introduced Linksz's inaugural volume on *Physiology of the Eye*. Finally he inspired the American Committee on Optics and Visual Physiology, of which he was chairman, to sponsor this present translation. Tschermak-Seysenegg deals with "physiologic optics" in a sense not currently used in English literature. No discussion of theoretical or applied optics, with the usual subheads of dioptrics, catoptrics, ametropia, accommodation, and presbyopia, is to be found. The scope of the book is restricted to what is designated by Duke-Elder in his *Textbook of Ophthalmology*, Volume I, Sections VII and VIII as the physiology and psychology of vision respectively.

Burian's sympathetic foreword stresses "that there is a subjective side to the functioning of the sense organs which can only be explored by subjective methods. . . . The most eminent representative of exact subjectivism—the man who has coined the term

—is Armin von Tschermak-Seysenegg."

The author details the unavoidable optical aberrations of the eye and finds that the principal factor in the retouching of the visual impression is physiologic contrast—that is, spatial and temporal induction. Goethe's intuitive conception is thus finally vindicated. The corrective quality of the contrast function has its limitations as exemplified in the illusion of irradiation. The limit of the light sense is determined by the contrast function and that of resolution by the dimensions of the retinal mosaic. The minimum visible and the minimum separable are hence separate entities. Night vision, color vision, and spatial vision are treated in a similar scholarly and original manner.

This is a work for the mature student. The budding ophthalmologist will find original English works in this field more assimilable, such as Linksz's recent and excellent *Vision*. The emphasis on extreme fidelity in the translation has hampered Boeder's usual grace and clarity, as was displayed so brilliantly in his *Mathematics of Ophthalmic Optics*. The reader is all too conscious that, though the text is English, the thinking is Teutonic.

James E. Lebensohn.

ADVANCES IN OPHTHALMOLOGY. Edited by E. B. Streiff (Lausanne). Basel, S. Karger, 1952, volume 1. 291 pages. Price: 39.50 Swiss francs.

Prior to 1943, the editors of the *Zeitschrift für Augenheilkunde* and of *Ophthalmologica* from time to time published reviews of ophthalmic literature that were extremely useful. World War II put a stop to this, and it is good to see that once more these valuable reviews are to appear every three to five years, with the treatment of each special subject by a competent specialist.

The present volume consists of a review from 1946 to 1950 of the treatment of concomitant strabismus by T. Keith Lyle; the

history of ophthalmology by G. ten Doeschate; methods of investigation by H. M. Dekking; optic nerve and chiasm by A. Biemond (in German); lens (including a review of cataract surgery by C. Heydacker) by J. Nordmann (in French); glaucoma by H. Goldmann (in German) which has a most complete bibliography for these years. The first three authors write in English.

It is learned that Volume 2 of this useful series is already in preparation and is to include chapters on the structure of the vitreous, electrophysiology of the eye, pathologic anatomy, the orbit, ocular injuries, and trachoma, each by well-known authorities.

Even for those who do not read French or German, the book is well worth owning for reference.

Derrick Vail.

basis in sound discipline. Her "identification" of elaborate patterns of microorganisms, nerve centers, "sex cells," geometric and alphabetic patterns in human and animal eyes probably stems from the aberrated shadows of *muscae volitantes*, vitreous micellae, and so forth. The illustrations are extremely primitive. Repetition of her observations is entertaining, and might be useful.

C. Keith Barnes.

TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA (British Medical Association), 1951, volume 11. Glebe (Seamer and Arundel Streets). Australian Publishing Company Limited. Price: \$5.00.

The presidential address delivered at Hobart congress by J. Bruce Hamilton briefly described some aspects of prevention of blindness in Australia and New Zealand.

Ida Mann pointed out that endocrine gland disorders may affect the eyes by causing: (1) Pathologic metabolism, (2) biochemical nerve stimulation, (3) changes from alteration of facial expression, (4) direct mechanical interference, and (5) psychologic changes. A large number of conditions involving the eyes, orbits, and eyelids are classified anatomically, and the influence of appropriate endocrine glands is explained.

Henrik Sjögren discussed the syndrome which he was the first to recognize. The earliest signs of keratoconjunctivitis sicca occur in the precorneal lacrimal film which becomes tougher and more viscous than normal. Later Bengal rose causes large stains, whereas small spots of staining may occur in many conjunctival diseases. Schirmer's test is a very unreliable test of lacrimal function. The main parts of the sicca syndrome are: keratoconjunctivitis sicca, xerostomia, and polyarthritis. Many diverse symptoms have been included, probably wrongly. The sicca syndrome is often incomplete. Familial

FORMULAS GRAFICAS PRACTICAS DEL VITA-OCULISCOPIO Y OCULISVITA. By Alice Larde de Venturino. Montevideo, Imp. Central, 1950. Paper covered, 28 pages, 17 illustrations. Price: Not listed.

In 1946, the author noticed that manipulation of spectacles before the eyes in various ways would permit her to use bright reflections for investigation of entoptic images. Direct rays from the sun, nonfluorescent light bulbs, and reflections from polished surfaces were then manipulated with lenses, pocket mirrors, rings, bottles, wine-glass bases, and numerous other sources of reflection to create magnified virtual images in space. She emphasizes the necessity of fixing the gaze on a minute brilliant spot (point-emission?) of light, and of securing magnification and focus by slight adjustments of the eye-reflector distance. (Although little physical explanation is given, she achieves a form of field-emission microscope within the eye, using light instead of electrons.)

Much of the brochure is devoted to her subjective opinions of the images, an admixture of fact and fantasy that extends beyond the bounds of credulity, with little

cases have been reported. The etiology is unknown. Therapy to be effective would have to be started before irreversible atrophy occurs in the lacrimal glands. Estrogens may be useful. Local treatment consists of restoring the moisture of the conjunctival sac. Obliteration of the canaliculi usually gives subjective relief.

A. Lister pointed out that the causes of congenital glaucoma are mechanical and arise in faults in the filtration angle. Descriptions and illustrations are used to differentiate normal from abnormal angles. There is always some enlargement of the affected eyes at birth but acute symptoms may be delayed. Filtration is grossly impaired in severe cases, but mild cases may have filtration almost adequate for normal demands. Goniotomy is most suitable for mild and early cases before the eye has become too damaged. Diagnosis is confirmed by examination under deep ether anesthesia. The author's contact lens is shown. The steps in goniotomy are described and, although a contact lens is not essential, one is preferred. The problem of severe and abnormal cases remains unsolved. Here the chances from any operation are poor. Every patient should be observed at intervals of not more than six months for the rest of life.

In a second essay Lister describes scleral resection in the treatment of retinal detachment. Diathermy fails in approximately 30 percent of retinal detachments. These include especially detachments in aphakic eyes, the absence of visible tear, multiple tears, and atrophic retina. Useful alternative methods are scleral resection and chemical coagulation by potash solution. Full-thickness scleral resection in semicircumference stages is preferred. With each resection potash solution was painted on the choroid but, in the absence of retinal hole, this procedure is probably not necessary. Single-armed interrupted sutures are inserted through the superficial scleral layers. For shallow detachments with fresh tears, a scleral trap door may be cut to

expose the choroid and potash solution injected between the sclera and choroid to cover the tear. The technique is described in detail.

Henrik Sjögren reports a retinal dystrophy occurring in five of a family of 13 children, called "dystrophia reticularis laminae pigmentosae retinae." Although the retinal pigment accumulates to form a peculiar network between the retinal vessels and around the maculas, the sensory layers of the retina are not disturbed and no subjective symptoms have occurred.

Kevin O'Day believes that a retinal cyst is a manifestation of necrosis of the retina following circulatory embarrassment. The causes may be: (1) The normally poor circulation in the retinal periphery, (2) trauma, leading to cysts and holes at the macula, (3) inflammation, and (4) vascular malformations and angiomas of the retina. Illustrative examples are given. Sections from an eye with familial retinal detachments are included.

W. D. Counsell presents a very condensed summary of knowledge of disorders of the oblique muscles under the following headings: Classification, diagnosis, surgical anatomy, possible operations, and indications for operation.

Emmie Russell states that the cover test is most useful, whereas synoptophore readings and other tests vary considerably on different days. Early surgery greatly reduces the time of orthoptic treatment. The latter is concerned mainly with diagnosis and strengthening of fusion.

Ivy Martyn found that patients with severe symptoms from convergence insufficiency may have an overacting inferior oblique muscle that only shows height difference as adductions develop. Symptoms are relieved and convergence ability is increased by measuring the height difference at 20 degrees on the synoptophore and ordering a prism base-up before the hypophoric eye.

R. Walkingshaw saw 4,246 patients at his out-patient clinic in Penang from July, 1950,

to June, 1951. Of these, 29 children had phlyctenular disease and 27 of them gave positive evidence of tuberculosis. The investigation supports the belief that phlyctenular disease of the eyes is one of the paratuberculous conditions.

Hugh Ryan observed 23 cases of retrolental fibroplasia in Melbourne from 1948 to 1950. All were in premature infants whose birth weight was under four pounds. There is a delay in coaptation of the layers of the retina in approximately 50 percent of premature babies who weigh less than three and one-half pounds at birth. This usually subsides but sometimes the detachment persists and increases in size. The maldevelopments are thought to be due to excessive administration of oxygen.

Ronald Lowe describes the differential diagnosis of facial twitching. Myokymia—fatigue twitching of the eyelids—and clonic facial spasm are considered in detail. Many of the antihistamine drugs have side reactions that include anti-acetylcholine properties. These may be used to produce a mild curariform effect and so diminish twitching of the facial muscles.

The sight-saving school at Hobart, Tasmania, is described by F. Phillips. It has 24 pupils, in six of whom the primary disability is nystagmus, four are highly myopic, two have ophthalmia neonatorum, and two are albinos. Controlled illumination, books with large print, and oral instruction are emphasized. The children often lack self-confidence and acting in plays is an important part of their education.

K. Barnden Brown points out that the presence of a small hole at the limbus precludes any negative pressure beneath the contact lens and so Sattler's veil is eliminated. The veil is the result of chemical suffocation caused by pressure on the conjunctival ves-

sels which brings about a deficiency of oxygen supplied to the cornea and the accumulation of carbon dioxide. The lens must be fitted exactly. Thirty-four patients with various conditions have been fitted so that all can wear their contact lenses without veiling throughout the whole of their waking life.

Ronald Lowe.

HEADACHES. By Stewart Wolf, M.D., and Harold G. Wolff, M.D. Boston, Little, Brown and Company, 1953. 174 pages. Price: \$2.50.

Written essentially for the layman, this treatise on a common complaint of mankind cannot help but be of interest to the ophthalmologist since headache is one of the most common symptoms to cause the patient to consult the ophthalmologist in the hope that glasses may cure his difficulty. Certainly refractive errors are by no means the most common cause of headaches; when the eyes have been eliminated as a factor in their production, the ophthalmologist should be able to advise his patient as to other possibilities. This book may be recommended to the layman who has been unable to receive relief from his distress.

In addition to a discussion of the mechanism of headaches, there are chapters on various organic and psychosomatic causes, with special emphasis on the latter. This is certainly justifiable since the majority of headaches are undoubtedly on a "nervous" basis. There is a brief discussion of headaches on an ocular basis, the only obvious error being the description of strabismus as a cause when phorias and vergence deficiencies should have been substituted. Glaucoma and other eye diseases are referred to briefly and probably adequately for a book of this type.

William A. Mann.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

1

ANATOMY, EMBRYOLOGY, AND COMPARATIVE OPHTHALMOLOGY

Genis Galvez, Jose M. **The presence of spiral nerve-endings in the orbicularis of the lids.** Arch. Soc. oftal. hispano-am. 12: 1327-1334, Nov., 1952.

The author demonstrated the presence in the orbicularis of the lids of spiral nerve endings like those found by Daniel in the extraocular muscles. (7 figures)

Ray K. Daily.

Henderson, Thomson. **The eye of the mole.** Brit. J. Ophth. 36:637, Nov., 1952.

(Entire article) The mole is commonly supposed not to possess any eyes. The persistence of this erroneous idea is not surprising, as the globe is 1 mm. in diameter and when the animal is skinned, the eyes adhere and come away with the pelt, leaving the sockets empty. After numerous attempts, a section has been obtained which goes through the pupil and optic nerve. The eye shows the features of arrested development in an embryonic stage. (1 figure)

Morris Kaplan.

Orts Llorca, F., and Genis Galvez, J. M. **Comparative volumetric study of the**

retinal nuclei of a human cyclopic embryo 22 mm. in size, and a normal embryo of similar size. Arch. Soc. oftal. hispano-am. 12:1202-1212, Oct., 1952.

The literature on biometric studies of cells of different organs and tissues and tissue cultures is reviewed. In this study the volume of the nuclei of the retina, the hypophysis, and rhombencephalon of a cyclopic embryo were compared with those of normal embryos of the same stage of development. The graphic illustration of the data shows that the retinal nuclei of the cyclopic eye are 69 percent larger than those of the normal embryo, and are subject to much greater variation. The increased volume of the nuclei of the monstrosity suggests that monstrosities have a genetic origin. The volume of the cell and nucleus is a constant characteristic of a species. (1 figure, 23 references)

Ray K. Daily.

Urtubey, L. **The orbital meninges.** Arch. Soc. oftal. hispano-am. 12:1261-1266, Nov., 1952.

In the hope of facilitating the understanding of the physiology of some of the ocular functions and the pathology of some of the ocular disturbances, the

author traces the relationship between the ocular structures and the cerebrospinal meninges, and tabulates the parts of the eyeball and the corresponding parts of the meninges. The portions of the retina closest to these protective coverings are not the ganglion layers, which contain the central neuron, but the sensory layers represented by the rods and cones. This arrangement is the result of the invagination of the optic cup in the course of the development of the eyeball from the central nervous system. In the optic vesicle, the position of the ocular structures corresponds to that of the other neuroaxial segments. In the mature eye the orbital periosteum corresponds to the periosteal layer of the dura, the epidural space of the spine to the orbital cavity, the sclera to the dura, the corneal endothelium to the arachnoid membrane, the anterior chamber to the subarachnoid space, the aqueous humor to the cerebrospinal fluid, the ciliary processes to the choroid plexus, the pigment layer of the retina to the chorioepithelium, and the retina to the brain. (1 table)

Ray K. Daily.

3

VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Barnett, A. J. **Ocular effects of methonium compounds.** *Brit. J. Ophth.* 36:593-602, Nov., 1952.

Pentamethonium and hexamethonium compounds have been used extensively in the treatment of arterial hypertension but little has been reported on the effects of these drugs on intra-ocular pressures. In this study seven patients with severe arterial hypertension were given intramuscular injections of 2 mg. per kg. of body weight and tonometric readings were made before and after injection. The effects were about the same after each drug. The ocular tension was reduced by 16 mm. Hg in one patient and 4.5 in an-

other and the average was 9.3 mm. Hg. This fall was apparent within 30 minutes and was still present at the last recording, in one patient 255 minutes after injection. The drug was given similarly to a patient with chronic glaucoma with a reduction in tension of about 20 mm. Hg. The mode of action of the drug has not yet been determined. The effect of continued administration of the drug has been noted in six patients with severe hypertension and marked retinal changes. There was absorption of soft exudates and hemorrhage in all of the patients and lessening of the papilledema which was present in five of the patients. This improvement in the retina is too striking to be the result of coincidence but the mode of action of the drug has not been ascertained. (4 figures, 3 tables, 9 references)

Morris Kaplan.

Belmonte Gonzalez, Nicolas. **Relative retinal hypotension.** *Arch. Soc. oftal. hispano-am.* 12:1266-1272, Nov., 1952.

Belmonte emphasizes the importance of determining the diastolic retinal pressure, and calls for a revision in our conception of the relationship between the retinal and brachial pressures. The accepted normal, a diastolic retinal pressure that is 50 percent of the brachial, is correct for young people, but represents a relative hypotension for the aged and particularly for aged hypertensives, in whom a diastolic retinal pressure that is 70 percent of the brachial pressure is required to maintain an adequate retinal circulation. He points out that in the course of preoperative examinations we frequently encounter hypertensives without symptoms of circulatory disturbances, with normal urinary findings, and normal blood urea. The fundus in these patients may show a marked arteriovenous compression, and white spots of capillarosis in the macular or peripapillary region. In these patients the increased blood pres-

sure is not pathologic, but serves to compensate for the rigidity of the vessel walls; the adequacy of the peripheral circulation is thus maintained despite a vascular sclerosis. The indiscriminate reduction of blood pressure in such cases is unsafe and may lead to failure of the peripheral circulation. Ray K. Daily.

Gallego, Antonio. **Electrophysiology of the retina.** Arch. Soc. oftal. hispano-am. 12:1150-1165, Oct., 1952.

The fundamental responses underlying electrical stimulation of the retina are explained. The electroretinogram is interpreted and the literature is reviewed. (9 figures) Ray K. Daily.

Gettes, B. C., and Leopold, I. H. **Evaluation of five new cycloplegic drugs.** A.M.A. Arch. Ophthalm. 49:24-27, Jan., 1953.

Five new cycloplegic drugs were tested on fair-skinned white persons and dark-skinned negroes. The effects of these drugs were compared on the basis of the amount of residual accommodation, recovery time, and action of standard drugs. Of the drugs tested, two were inadequate cycloplegics for routine use, bantnine and D-2 methobromide. The remaining three had a more profound effect than 4-percent homatropine combined with 1-percent paredrine. These three compounds were related esters of disubstituted acetic acid known as Compounds 75 G.T., 92 G.T., and 93 G.T. (2 tables, 11 references)

George S. Tyner.

Grom, C. Edward. **The relation between the retinal vascular pressure and the intraocular pressure.** Arch. Soc. oftal. hispano-am. 12:1273-1290, Nov., 1952.

The author analyses the physiologic and pathologic relationship between the arterial retinal and the intraocular pressures. He distinguishes four types of this relationship. 1. Both at the physiologic level. The intraocular pressure is 16 to

42 mm. Hg; the diastolic retinal pressure is 50 percent of the brachial pressure; the retinal systolic pressure is 70 percent of the brachial pressure. 2. The vascular retinal pressure is abnormally high in proportion to the intraocular pressure; the vascular tension may be normal and the ocular low or the vascular pressure may be high and the intraocular low; this state leads to vascular retinal lesions, hyperemia or hemorrhage. 3. The vascular retinal pressure is abnormally low in comparison with the intraocular pressure; low vascular retinal and intraocular pressure may explain glaucoma without hypertension. The vascular retinal pressure may be normal and the intraocular pressure high. The vascular retinal pressure may be low and the intraocular pressure high; these are the most unfavorable cases, with ready development of nutritive and circulatory disturbances in the retina and optic disc. 4. The retinal vascular and intraocular pressure proportionate, but abnormally high or low. In the first event we find patients who tolerate well an increased intraocular pressure. The low pressures are encountered in shock. The author urges that the retinal vascular pressure of patients with glaucoma be studied, in order to avoid introducing a disturbance in the relationship between the arterial retinal and the intraocular pressure by medication or surgical procedures. (25 references)

Ray K. Daily.

Heinsius, E., and Hallmann, L. **The topical application of modern antibiotics.** Klin. Monatsbl. f. Augenh. 122:68-76, 1953.

This work deals with experiments and clinical experiences with Tyrosolvin, a water soluble preparation of tyrocidin. After subconjunctival or intracorneal injections of staphylococci or streptococci, Tyrosolvin cleared the eyes quickly. The results were equivocal after injection of

pneumococci. The in vitro experiments revealed a wide spectrum for this drug. Hypersensitivity to it has not been observed. (1 figure, 1 table, 22 references)

Frederick C. Blodi.

Kleinert, Heinz. **The frequency of post-operative hemorrhage of the anterior chamber after cataract extraction after glutaminic acid.** *Wien. med. Wchnschr.* 103:132-134, Feb., 1953.

If minimal bleeding is included, the incidence of hemorrhage into the anterior chamber after cataract extraction was not influenced by 0.5 gm. glutaminic acid given prophylactically twice daily, but the number of hemorrhages severe enough to necessitate paracentesis was reduced to half. The effect could be ascribed to increased capillary resistance. The drug might also bring about a beneficial change in the metabolism of the aged cerebrum which enables the patient to cooperate more deftly and avoid action which brings about hemorrhage.

F. H. Haessler.

Thiel, H. L. **Tyrosolvin, a new antibiotic.** *Klin. Monatsbl. f. Augenh.* 122:76-78, 1953.

Tyrosolvin is a water soluble preparation of tyrocidin. It was found to be of value in the treatment of acute and chronic conjunctivitis, and corneal ulcers and infiltrates. It was especially successful in clearing the conjunctival sac of pathogenic microorganisms preoperatively, when other drugs had failed. (5 references)

Frederick C. Blodi.

4

PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Hirsch, Monroe J. **Sex differences in the incidence of various grades of myopia.** *Am. J. Optometry* 30:135-138, March, 1953.

Of 5,201 patients aged 18 to 50 years,

examined at the Los Angeles College of Optometry, 2,048 were myopic. Of those with less than 6.00 diopters (average of sphere and cylinder in both eyes), 1,082 were men, 929 were women. Of those with more than 6.00 diopters, 11 were men and 26 were women. Simple myopia is therefore considered more common in men, and degenerative myopia more common in women.

Paul W. Miles.

Schulte, Dieter. **Improved contact glasses with a hole in the corneal part.** *Klin. Monatsbl. f. Augenh.* 121:673-683, 1952.

Holes at the margin of the corneal part of a contact lens facilitate an exchange between the fluid beneath the lens and the tears. In this way patients can wear these modified Zeiss lenses much better and longer. (1 figure, 15 references)

Frederick C. Blodi.

Stone, L. S. **Normal and reversed vision in transplanted eyes.** *A.M.A. Arch. Ophth.* 49:28-35, Jan., 1953.

Experiments with amphibian eyes have demonstrated that the neural retina is regenerated from retinal pigment epithelium in this class of vertebrates. When the neural retina is separated from the underlying pigment epithelium and removed surgically, regeneration of the neural elements takes place in three to four months. The retinal pigment layer itself can be detached and implanted into the aqueous chamber of a host animal and give rise to neural retina and visual function. The eyes of a number of species of salamander can be transferred to a host of an entirely different species and become functional visual organs. Transplantation studies have shown that retinal fields are re-established as they were originally, and function according to their orientation. Thus in a transplanted eye rotated 180 degrees from its normal position, or a right eye transferred to a left

orbit, the retinal quadrants retain their original spatial orientation. (3 figures, 11 references)

George S. Tyner.

Tait, Edwin F. A quantitative system of dynamic skiametry. *Am. J. Optometry* 30:113-129, March, 1953.

This is a review of 25 years' work by Dr. Tait and others on a refractive procedure which is not in common use by ophthalmologists. He concludes that objective refraction of any accuracy is limited to the results obtained by the ophthalmometer and the skiascope. Any subjective test is altered by habit and psychic factors influencing the patient's judgment. There is an accommodative lag in near vision which varies with the method of measurement, but can supply valuable diagnostic information about the accommodation-convergence reflex.

Paul W. Miles.

5

DIAGNOSIS AND THERAPY

Agarwal, L. P., and Mathur, S. P. Curare in ocular surgery. *Brit. J. Ophth.* 36:603-610, Nov., 1952.

Curare is particularly useful in ocular surgery in that the ocular muscles are among the first to be affected and the last to recover. The muscular spasm resulting from fear, apprehension or pain can be easily controlled. Vitreous loss in cataract surgery has been unquestionably reduced. The drug is especially indicated in nervous, apprehensive, or deaf patients and those who have senile dementia and it is contra-indicated in those with myasthenia gravis, renal disease, asthma or recent respiratory disease. About $\frac{1}{2}$ unit per pound of body weight is given intravenously at the rate of 20 units per minute and is administered with the usual preoperative medication and topical anesthesia. The drug is excreted in 25 to 30 minutes and the patient can then walk

back to bed unassisted. In this study, 25 patients, from 40 to 66 years of age, were given d-tubo-curarine successfully for cataract surgery and with no untoward effects. (3 tables, 8 references)

Morris Kaplan.

Arruga, Alfredo. A device for the demonstration of the deviation in motor ocular disturbances. *Arch. Soc. oftal. hispano-am.* 12:1344-1349, Nov., 1952.

After a discussion of the merits and disadvantages of the Hess and Lancaster devices for measuring the deviation in cases of ocular paralysis, Arruga describes a screen which he devised for the same purpose. It is similar to the Hess screen and has 25 perforations illuminated from behind. The patient is asked to cover these with a green light projected from a hand light. (4 figures, 4 references)

Ray K. Daily.

Bietti, G. B. The role of plastic material in ocular surgery. *Rassegna internat. di clinica e terapia* 33:41-48, 1953.

Acrylic and polyethylene are discussed. These plastics have been found useful as implants after enucleation, for filling skeletal defects in the orbit, for recanalization of the lacrimal duct, as artificial cornea or lens and as drainage in cyclo-dialysis or after an operation for retinal detachment.

Frederick C. Blodi.

Bounds, George W., Jr. The electroretinogram. *A.M.A. Arch. Ophth.* 49:63-89, Jan., 1953.

This is an extensive review of the past and present literature on the subject including an historical note, the physiologic basis of the electroretinogram, and a description of the apparatus and its use. The normal and the abnormal retinograms in various ocular diseases are described. (10 figures, 2 tables, 89 references)

George S. Tyner.

Condon, H. A. **General anesthesia in ophthalmic surgery.** *Brit. J. Ophth.* 36: 611-614, Nov., 1952.

Condon has preferred the routine use of general anesthesia and has had no cause to return to local anesthesia. In this report the last 200 cases are very briefly described; all of the usual surgical procedures are represented and patients were from 9 weeks to 90 years of age. For the brief procedures, ethyl chloralhydrate or nitrous oxide are given and for the longer ones thiopentone with nitrous oxide and oxygen; intubation is always used. Surgical complications have been considerably fewer and general anesthesia has been entirely satisfactory. The use of curare seems quite unjustified. (1 figure, 2 tables, 14 references) Morris Kaplan.

Goldsmith, H. **Modified Castroviejo's forceps.** *Brit. J. Ophth.* 36:654-655, Nov., 1952.

The Castroviejo cross-action cataract forceps is modified by making the lower half heavier than the upper and by adding serrations along the lower third. (1 figure) Morris Kaplan.

Harms, H. **The practical importance of quantitative perimetry.** *Klin. Monatsbl. f. Augenh.* 121:683-692, 1952.

The author emphasizes the advantages of quantitative perimetry which measures the light sense. In this method the size of the target remains unchanged while its illumination is decreased. The author's targets are observed under a visual angle of ten minutes in contrast to Sloane, who first advised this form of perimetry. Models of this perimetric island were constructed. Relative central scotoma may be found more easily with this method. (9 figures, 8 references)

Frederick C. Blodi.

Munoz, Luis. **A serious secondary hemorrhage following extirpation of a**

chalazion. *Arch. Soc. oftal. hispano-am.* 12:1317-1320, Nov., 1952.

A man, 18 years old, with healed tuberculosis and juvenile diabetes under control, was operated on for chalazion. One suture was used and it was removed six days after the operation. Two days later hemorrhage occurred due probably to the sloughing of a small necrotic area. The hemorrhage could not be controlled by a compressive bandage, and local and general hemostatics, including a transfusion. It was finally checked by a U suture, which tied the bleeding palpebral arteriole. This case points to the necessity of continuous vigilance after surgery on a diabetic, even when well controlled, because even a mild emotional disturbance may upset the sugar metabolism. It also shows the superiority of a suture over other methods of hemostasis. (8 references) Ray K. Daily.

Posada Ponseca, Alejandro. **Transilluminator with perforating diathermy, for surgery of retinal detachment.** *Arch. Soc. oftal. hispano-am.* 12:1197-1201, Oct., 1952.

The author describes a transilluminator, the handle of which also contains a perforating diathermy electrode. The point of the perforating needle comes out of the tip of the transilluminator when a control button is pressed at the other end of the handle, and recedes back into the interior of the transilluminator when the pressure on the control button is released. The advantage claimed for the instrument is the possibility of making the electrocoagulating punctures under direct observation with the ophthalmoscope, and thus limiting the number of punctures, which is of decided advantages in holes in and about the macula. (3 figures) Ray K. Daily.

Remler, O. **A combined intravenous anesthesia in ophthalmology.** *Klin.*

Monatsbl. f. Augenh. 122:63-67, 1953.

A combination of demerol and pentothal has been successfully used in a variety of ocular operations. (7 references)
Frederick C. Blodi.

Rieger, H. **The evaluation of the tests for toxoplasmosis in ophthalmology.** Klin. Monatsbl. f. Augenh. 122:11-25, 1953.

This is a survey and a critical evaluation of the skin test, the dye test, and the complement fixation test. The author follows Sabin very closely without offering anything new. He emphasizes the fallacies of a single serological test which has led him to erroneous clinical diagnoses in the past years. (43 references)

Frederick C. Blodi.

Schober, Herbert. **Heterophoria and irradiation test with the projecto-chart.** Klin. Monatsbl. f. Augenh. 121:717-718, 1952.

Heterophoria can be tested by the use of a chart which has a green cross in a red circle. The patient must wear a red glass before one eye and a green glass before the other. Irradiation sensitivity can be tested with the white hook of Pflueger. (1 reference)

Frederick C. Blodi.

6

OCULAR MOTILITY

Adelung, J. C. **Results of graduated advancement and recession according to Kunz.** Klin. Monatsbl. f. Augenh. 121:700-707, 1952.

Kunz advised the symmetrical advancement and recession operation. The author had better results with this graduated method than with a simple tenotomy or advancement. (1 table, 18 references)

Frederick C. Blodi.

Spaeth, Edmund B. **Surgical aspects of defective abduction.** A.M.A. Arch. Ophth. 49:49-62, Jan., 1953.

Four causes of defective abduction of the globe are described and surgical treatment discussed. In Duane's retraction syndrome, tendon transplantation is futile. Surgical treatment should consist of recession of the medial rectus and exploration of the external rectus with release of fascial bands. In strabismus fixus, the fibrosed internal rectus is recessed or tenotomized. In congenital sixth nerve paralysis, recession of the internal rectus muscle combined with resection of the external rectus or tendon transplantation is indicated. In acquired sixth nerve paralysis surgery should be postponed for at least 12 months. The procedure of choice is tendon transplantation. The author stresses the need for careful pre-operative evaluation and avoiding over-optimism with regard to expected results. (15 figures, 6 references)

George S. Tyner.

7

CONJUNCTIVA, CORNEA, SCLERA

Barraquer Cerero, Tomas. **Blepharoconjunctival allergy.** Arch. Soc. oftal. hispano-am. 12:1321-1326, Nov., 1952.

The objective of this presentation is to describe a clinical experience and to revise our conception of the conjunctival flora and of conjunctival reactions. The author has encountered many cases of low-grade chronic conjunctivitis resistant to all forms of therapy, and particularly intolerant of therapy with zinc solutions. At times such inflammation improved under some form of therapy, only to recur after a short time. Bacteriologic studies of the conjunctiva and nasal passages revealed the following germs in the following order of frequency: the staphylococcus, the streptococcus, the pseudodiphtheria bacillus, and the pneumococcus. Satisfactory results were obtained in these patients only after autovaccine therapy was added to treatment with antibiotics. The author believes that

the affection may be caused by sensitization to staphylococci in a distant focus, such as the sinuses, the seminal vesicles, or a focus in the lungs. He feels that, except by Thygeson, the importance of the staphylococcus as a pathogenic conjunctival organism is not sufficiently appreciated.

Ray K. Daily.

Beckett, H. C. **Bilateral congenital anterior staphyloma treated by keratoplasty.** *M. J. Australia* 1:372-373, March, 1953.

A child, age six years, with bilateral congenital anterior staphyloma developed glaucoma and both corneas became perforated. Cyclodialysis and 10-millimetre penetrating keratoplasty were performed on each eye and bilateral enucleation was avoided. Both lenses were opaque and shrunken. The child can recognize colors and distinguish moving vehicles at a distance of 30 feet. Ronald Lowe.

Bickel, H., Smallwood, W. C., Smellie, J. M., Barr, H. S., and Hickman, E. M. **Cystine storage disease with aminoaciduria and dwarfism (Lignac-Fanconi disease).** *Acta Paediatrica* 42, Suppl. 90, pp. 1-237, 1952.

Lignac-Fanconi disease is a genetic thesaurismosis, probably of simple Mendelian recessive character. Cystine storage can be demonstrated in vivo by slit-lamp study of the cornea and conjunctiva. The ophthalmologist will find this monograph an excellent repository of the information he will need when he recognizes the corneal change.

F. H. Haessler.

Fernandez-Repeto, Santiago. **Double pterygia.** *Arch. Soc. oftal. hispano-am.* 12:1310-1316, Nov., 1952.

This review of the literature on the subject was made when the author's interest was aroused by a case found in the course of an examination for an industrial injury. (1 figure)

Ray K. Daily.

Friede, Reinhard. **Penetrating keratoplasty with a Descemet-margin.** *Klin. Monatsbl. f. Augenh.* 121:692-696, 1952.

The author advises to trephine only down to Descemet's membrane. The latter is then perforated and the central piece is excised. In this way a marginal shelf of membrane remains onto which the graft is placed. This gives a better protection against the aqueous at the border. (2 figures)

Frederick C. Blodi.

Gezurian, Z. L. **The infectious agent in Sjögren's syndrome.** *Arch. oftal. Buenos Aires* 27:265-267, June, 1952.

In a previous paper the author had discussed Sjögren's syndrome as an affection of the serous glandular system. Now he discusses the infectious element in that syndrome, and concludes that the latter is only secondary to the serous glandular dysfunctions. J. I. Pascal.

Jakober, Otto. **The treatment of conjunctivitis and trachoma in eastern Iran.** *Klin. Monatsbl. f. Augenh.* 122:90-93, 1953.

The author uses Supronal with great success. For the treatment of trachoma he advises electrocoagulation. (3 figures)

Frederick C. Blodi.

Nonnenmacher, Heinz. **The treatment of progressive sclero-perikeratitis.** *Klin. Monatsbl. f. Augenh.* 121:707-712, 1952.

This case of brawny scleritis responded well and rapidly to irradiation. The lacrimal gland was also affected. There was no sign of tuberculous infection when the tissues were examined at autopsy. (19 references)

Frederick C. Blodi.

Rio Cabanas, Jose L. **The present status of pterygium surgery.** *Arch. Soc. oftal. hispano-am.* 12:1298-1309, Nov., 1952.

The voluminous literature on the subject is reviewed. In the author's own ex-

perience with the invading and progressive type of pterygium the best results were obtained by placing a conjunctival flap over the site of the pterygium, after the latter had been excised. The results were the same, whether the conjunctival flap was obtained by traction, torsion, or was free. The author is experimenting with conjunctival flaps from cadavers.

Ray K. Daily.

Rosenthal, J. William. **Beta-radiation therapy of pterygium.** A.M.A. Arch. Ophth. 49:17-23, Jan., 1953.

This is a report of the treatment of pterygium in 85 eyes; 42 were treated surgically and 43 with beta irradiation. The Swanberg 10-mc. applicator was used in all the beta-treated eyes. In the cases treated surgically the McReynolds technique was employed in 33 cases, the Blaskovics in 9, and the Hobby in 1. Surgical treatment failed in 15 percent and beta-radiation in 19 percent. The approximate total optimum dose of irradiation was 5 mc.-hr. for heavy ptergia and 2.5 mc.-hr. for flatter membranous types. The treatment of choice for pterygium is the McReynolds transplantation followed within one week by application of the radium D applicator. (2 figures, 1 reference)

George S. Tyner.

Ruedemann, Albert D., Jr. **Osteogenesis imperfecta congenita and blue sclerotics.** A.M.A. Arch. Ophth. 49:6-16, Jan., 1953.

The pathologic changes in the eyes of three patients with osteogenesis imperfecta are reported. This disease is characterized by bone fragility, blue sclera, otosclerosis with deafness, relaxation of ligaments and skeletal muscles, dental and other defects. Examination of sections of these eyes disclosed the following defects: a general deficiency of collagen giving rise to scleral thinning (hence the "blue" color), juvenile glaucoma in one

case, enlargement of the globes in another case, and retention of immature precollagenous reticulum fibers. (6 figures, 23 references)

George S. Tyner

Velhagen, Karl, Jr. **Argyrosis of the cornea.** Klin. Monatsbl. f. Augenh. 122: 36-42, 1953.

The author reports a case of bilateral argyrosis of the cornea and the conjunctiva after prolonged use of a dye for the lashes. This dye was an aqueous solution of a silver salt. (1 figure, 50 references)

Frederick C. Blodi.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Busacca, A., Nobrega, P., and Giovannoni, M. **Clinical and experimental investigations on toxoplasmosis with ocular localization.** Arch. d'ophth. 12:681-691, 1952.

In serological studies in which they used toxoplasmosis antigen and the complement-fixation test, Busacca and associates found that 28.5 percent of adult patients with active chorioretinitis were positive in contrast to 3 percent of normal subjects. On the basis of statistical analysis they concluded that a certain number of adult chorioretinitis cases must be of toxoplasmic origin, but they concluded further that in any individual case the diagnosis could be presumptive only since there are no specific clinical signs. In experimental studies they found that aqueous derived from three cases of active chorioretinitis with high serological titers failed to infect mice. As a result of experimental infection of adult pigeons with a strain of toxoplasmosis, one bird, at the end of the second month, developed ocular lesions which were limited to the posterior segment and closely resembled human toxoplasmic chorioretinitis. Parasites in the form of pseudocysts were

numerous. The authors believe that the pigeon offers promising possibilities for the study of experimental ocular toxoplasmic lesions. (10 figures)

P. Thygeson.

Chin, Lein-Chung, and Kung, Yü-Peh. **Choroiditis proliferans.** Chinese M. J. 70: 162-166, March-April, 1952.

A case of choroiditis proliferans is described in a Chinese woman with trachoma, hypertensive retinopathy, and simple optic atrophy. (2 figures, 8 references)

Irwin E. Gaynon.

Huerkamp, B. **Two types of essential atrophy of the iris.** Klin. Monatsbl. f. Augenh. 121:654-662, 1952.

On the basis of three personal observations and of the cases reported in the literature, the author divides essential iris atrophy into two distinct groups. The first type occurs frequently in women in the third decade of life. Usually only one eye is affected and the atrophy begins in the periphery leading to a hole in the iris and to a change in the contour of the pupil. Glaucoma occurs early. The second type affects both eyes and occurs more frequently in men during the fifth decade. It progresses as an enlargement of the pupil. Myopia and choroidoretinal atrophies lead early to visual impairment. Vascular disturbances probably cause both types of iris atrophy. (1 table, 3 figures, 54 references)

Frederick C. Blodi.

Pietruschka, Georg. **Changes of the iris in neurofibromatosis.** Klin. Monatsbl. f. Augenh. 121:663-672, 1952.

Small neurofibromas have frequently been observed in the iris of patients with neurofibromatosis. Among 31 patients with known neurofibromatosis, the typical small neurofibromas of the iris could be found in 26 patients. These little tumors are round or oval, well circumscribed and

prominent. No pathologic verifications are presented. (5 figures, 16 references)

Frederick C. Blodi.

Pillat, A. **The clinical picture of an inflammation of the vortex veins.** Klin. Monatsbl. f. Augenh. 122:1-11, 1953.

This is the first clinical description of a case of periphlebitis of the vortex veins. The ophthalmoscopic examination showed radial, elongated, pigmented lesions at the equator in the characteristic meridians. These lesions were first seen in a 24-year-old woman and could be observed for 15 years. The cause was a tuberculous cyclitis. (1 figure, 4 references)

Frederick C. Blodi.

Schum, R. **The formation of a pupil in an occlusion membrane of an aphakic eye.** Klin. Monatsbl. f. Augenh. 121:696-700, 1952.

The author had good results when making a central corneal incision with a knife. Through this incision the iris is grasped, pulled out and excised. (3 figures)

Frederick C. Blodi.

Thomson, A. M. Wright. **Infantile choroido-retinal degeneration with cerebral symptoms.** Brit. J. Ophth. 36:649-652, Nov., 1952.

Most choroidoretinal degeneration in children is due to toxoplasmosis the presence of which is shown by serologic tests for the parasite as well as the presence of cerebral calcification as shown in X-ray studies of the skull. A patient is described in whom the fundus lesions closely resembled those of toxoplasmosis with accompanying progressive cerebral degeneration. Serologic tests and X-ray studies of the skull were negative in the mother and the child although evidence of internal hydrocephalus was seen. The cause of the condition could not be determined. (1 figure, 2 references)

Morris Kaplan.

9

GLAUCOMA AND OCULAR TENSION

Barkan, Otto. **Goniotomy for glaucoma associated with aniridia.** A.M.A. Arch. Ophth. **49**:1-5, Jan., 1953.

The author reports the first successful goniotomy in a case of glaucoma due to congenital aniridia. He explains the mechanism of glaucoma in aniridia as a result of obstruction of the anterior chamber angle from adhesions between the rudimentary iris tissue and Schwalbe's line. Residual embryonic tissue in the angle pulls the rudimentary iris toward Schwalbe's line, thus sealing off the angle. (2 figures, 9 references) George S. Tyner.

Bietti, G. B. **Plastic drainage in cyclodialysis.** L'Ateneo parmense **23**: pp. 8, 1952.

The success of a cyclodialysis depends on the open cleft which drains aqueous into the suprachoroidal space. A permanent drainage can be assured by the introduction of a foreign body that will keep the cleft open. The author tried a polyethylene tube as a drain after cyclodialysis in rabbits. The plastic material was well tolerated. This method of operation was then performed on four human eyes with encouraging results.

Frederick C. Blodi.

Bietti, G. B. **Goniotomy in hydrophthalmos.** L'Ateneo parmense **23**: pp. 8, 1952.

The author discusses various goniotomy operations, especially goniotomy. Out of 15 eyes, 11 were permanently stabilized as far as pressure was concerned. These operations are harmless and should be tried as a first procedure in hydrophthalmos.

Frederick C. Blodi.

Kleinert, Heinz. **Tension and rigidity of the eye.** Klin. Monatsbl. f. Augenh. **122**:51-63, 1953.

This is a review on Friedenwald's work on scleral rigidity and the rigidity coefficient. The author determined the diurnal curves of the rigidity coefficient and of the true intraocular pressure (calculated according to Friedenwald). In all cases he found an increase in the rigidity coefficient when the pressure rose and vice versa. Such a relationship was not present when the increased pressure was artificially induced. The changes in the rigidity are therefore not the sequelae of the increased intraocular pressure. They may be caused by an edema of the sclera. A similar process may involve the meshwork of the angle and embarrass the outflow of the aqueous. (2 figures, 23 references)

Frederick C. Blodi.

Loesche, W. **Improvement of cyclodialysis.** Klin. Monatsbl. f. Augenh. **121**:715-716, 1952.

The author advises an iridectomy through a hollow spatula or the implantation of a plastic tube to guarantee internal fistulation. Frederick C. Blodi.

Nisbet, Alfred A. **Glaucoma in aphakia.** Texas State J. Med. **49**:134-137, March, 1953.

The etiology of glaucoma in aphakia is discussed from the standpoint of iridocyclitis after extracapsular cataract extraction, iris incarceration, delayed anterior chamber formation and epithelial ingrowth. Intracapsular cataract extraction with a round pupil, iridotomy, and appositional corneoscleral sutures are advocated. (6 references)

Irwin E. Gaynon.

Pallares, J. **Some modifications in the details of Stallard's operation for glaucoma.** Arch. Soc. oftal. hispano-am. **12**: 1178-1188, Oct., 1952.

Pallares is very enthusiastic over the results of Stallard's operation, which prizes an anterior trap-door sclerotomy

and a basal iridencleisis, in chronic as well as in acute inflammatory glaucoma. The modifications which he describes are 1. the insertion of a traction suture anterior to the sclerotomy incision, and fixation of the posterior lip of the incision by a loop; 2. section of the deeper scleral layers by a probe-tipped knife, such as a Weber canaliculus knife; 3. rolling of the conjunctival flap over a small triangular file, to improve the visibility of the angle of the anterior chamber; and 4. the use of de Wecker scissors with blunt tips to fashion the triangular flap of iris for inclusion in the lips of the wound. The purpose of the modification is to make the operation easier. (13 figures) Ray K. Daily.

10

CRYSTALLINE LENS

Burch, E. P. **Advances in cataract surgery.** *Minnesota Med.* 35:1149-1150, Dec., 1952.

It has recently been demonstrated that 1-percent xylocaine is an excellent anesthetic agent for deep orbital injection and akinesia of the lids. Xylocaine as well as novocaine may be combined with either epinephrine or hyaluronidase, or both. The impression has been gained that if an intracapsular extraction is planned, xylocaine may be superior to novocaine, since marked hypotony, together with excellent ciliary ganglion and motor block and akinesia, has been noted in a very high percentage of cataract patients receiving xylocaine. The single most important technical improvement in the extraction of the lens is the almost universal use of some type of corneoscleral suture, either with or without a conjunctival flap. Both chromic catgut and black silk sutures are being used. The corneoscleral suture permits more freedom in bed, earlier ambulation and discharge from the hospital. It has rendered postoperative occlusion of both eyes unces-

sary. Corneoscleral sutures lessen the threat of iris prolapse. They reduce the amount of astigmatism, promote earlier reformation of the anterior chamber, and decrease the incidence of hemorrhage into the anterior chamber. Such sutures permit the preservation of a round pupil in the majority of operations for cataract. The chief advantage of absorbable mildly chromicized, catgut sutures over silk is that the removal of the latter type is always attended by a slight but ever-present risk. Since the advent of the sulfa drugs and the antibiotics, potent agents are available to sterilize the conjunctival sac before operation and to combat infection in the untoward event of postoperative infection. Cortisone can be of great value in checking postoperative iritis, particularly that variety which is due to retained lens substance following extracapsular extraction. Theodore M. Shapira.

Hallermann, W. **The etiology of brown, lamellar cataract.** *Klin. Monatsbl. f. Augenh.* 121:641-647, 1952.

This type of cataract, first described by Vogt, is a yellow or brownish lamellar cataract at the posterior margin of the embryonal nucleus. Fifteen cases have so far been described and eleven occurred in syphilitic patients. The situation of the opacity requires a prenatal infection. The author describes another case in which the cataract was unilateral. The same eye showed the residues of an interstitial keratitis, and the fundus gave the picture of a severe chorioretinitis. The serologic tests for lues were strongly positive. This case is further evidence for the assumption that this type of cataract is a complicated cataract due to an intrauterine infection, usually syphilis. (3 figures, 14 references) Frederick C. Blodi.

Hirsch, F. G., and Parker, J. T. **Bilateral lenticular opacities occurring in a technician operating a microwave genera-**

tor. A.M.A. Arch. Indust. Hyg. 6:512-517, Dec., 1952.

A case of bilateral nuclear lenticular opacities with acute chorioretinitis in the left eye in a technician operating a microwave generator is reported. Personnel in daily contact with the energy dissipation of rays of microwave generators should wear metallic spectacle frames in which a fine copper mesh has been substituted for the ordinary lens. (3 figures)

Irwin E. Gaynon.

Malbran, Jorge. **Refinements in cataract extraction.** Arch. Soc. oftal. hispano-am. 12:1251-1259, Nov., 1952.

The essentials of Malbran's technique comprise a Van Lint akinesis, a retrobulbar injection, retraction of the lids with Castroviejo's mosquito clamps, preplaced corneal sutures, a strictly corneal section, and extraction of the lens by suction or forceps. He has discontinued the use of a bridle suture, and does not disturb the integrity of the iris. (3 figures, 14 references)

Ray K. Daily.

Remler, O. **The brown, lamellar cataract.** Klin. Monatsbl. f. Augenh. 121:647-653, 1952.

This type of cataract occupies the posterior margin of the embryonal nucleus. The author observed 22 cases at the clinic in Frankfurt. Twelve patients had a definite syphilitic infection. No etiology for this type of embryonal cataract was found in the other ten patients. It must be assumed that other intrauterine infections or prenatal disorders may produce these lens changes. (1 table, 1 figure, 8 references)

Frederick C. Blodi.

11

RETINA AND VITREOUS

Begg, N. C., and Wilson, R. P. **Retro-lental fibroplasia.** New Zealand M. J. 52: 30-34, Feb., 1953.

The first case of retrolental fibroplasia

in New Zealand is reported. The mother suffered from Addison's anemia throughout pregnancy. The infant's birth weight was 2 pounds and 1 ounce. Pemphigus developed after delivery. The cicatricial stage of retrolental fibroplasia was first noted at 7½ months of age. It is inadvisable to use too much oxygen. (12 references)

Irwin E. Gaynon.

Cramer, Federico E. K. **Alterations in the fundus of the eye in tuberculous meningitis in children treated with streptomycin.** Arch. oftal. Buenos Aires 27:251-264, June, 1952.

Observation of 54 patients led to several conclusions. Tuberculous meningitis in children shows alterations in the fundus in 82 percent and these are easily recognized with the ophthalmoscope. There are no typical ocular manifestations of the disease, but the changes noted make the diagnosis quite certain. The lesions found were 1. choroidal or chorioretinal, and 2. papillary. Choroidal lesions (choroidal tubercles of Bouchut) were found in 9 percent of the cases. Alterations in the papilla were found in 72 percent and were 1. vasomotor changes (hyperemia and ischemia); 2. edema of the papilla; and 3. ectasia of the papilla. The survival of the patients after treatment with streptomycin has made it possible to study the evolution of the ocular lesions and their final state. As the patients get well, the ophthalmoscope frequently shows a return to normal of the fundus, but at times there is partial or total papillary atrophy. The ocular lesions frequently do not correspond to the gravity of the disease. It is important to make frequent ophthalmoscopic examination, not only in the patient on the road to recovery in order to confirm the favorable prognosis, but also in order to foresee an approaching relapse from changes, particularly edema in the papilla. Ophthalmoscopic examination of patients

with bacillary meningitis should be made routinely and often, since this has proved its value for diagnosis and prognosis.

J. I. Pascal.

Csapody, I., and Kovacs, A. **X-ray treatment for retinoblastoma.** *Klin. Monatsbl. f. Augenh.* **122**:43-51, 1953.

A retinoblastoma in the second eye, successfully treated by irradiation according to Reese, is reported. (5 figures, 9 references)

Frederick C. Blodi.

Fanta, H. **Further histologic studies of the sclera after shortening operations.** *Klin. Monatsbl. f. Augenh.* **122**:25-36, 1953.

This histologic study is mainly based on scarred stripes of sclera excised after a repeated shortening operation. It is necessary to close the scleral wound with many silk sutures to avoid its opening and it takes years before these sutures become absorbed. They may cause necrosis and inflammatory reaction. The scar tissue is formed by the episcleral tissue. (11 figures, 5 references)

Frederick C. Blodi.

Havenar, W. H., and Falls, H. F. **Liptopic treatment of vitreous opacities.** *Univ. Michigan Med. Bull.* **19**:12-13, Jan., 1953.

Intravitreally injected cholesterol in rabbits was not affected by the use of Methiscol capsules and Lipozyme tablets. The vitreous opacities remained the same after five months of very intensive treatment.

Irwin E. Gaynon.

Larmande, A., Toulant, M., and Timsit, E. **Infero-version of the retina.** *Arch. d'opht.* **12**:692-698, 1952.

The authors note the rarity of infero-version of the retina and describe a case in a 27-year-old Arab. The retinal detachment, which involved the entire upper half, occurred six weeks after a knife injury that had perforated the left cornea

near the limbus at 5 o'clock. The disc was covered by the retina which had become detached to its border. In the lower nasal quadrant a portion of the anterior surface of the detachment could be seen. There was no return of the retina to normal position on bed rest and no surgery was attempted. The clinical picture is well illustrated by a drawing in color. From a review of the literature the authors conclude that the condition occurs most commonly in young adults and that it follows recent injury. They consider the prognosis totally unfavorable but mention the one case described by Goldenberg in which a temporary spontaneous reattachment occurred. (1 figure, 16 references)

P. Thygeson.

Levy, Jack. **Inherited retinal detachment.** *Brit. J. Ophth.* **36**:626-636, Nov., 1952.

Although most familial retinal detachment is associated with high myopia, most of the cases presented here occurred in hyperopic subjects. Two pedigrees are described in which the disease follows the x-chromosomal inheritance pattern. In one of them the abnormality occurred in seven males but was transmitted by females without retinal detachment and five subjects had other ocular abnormalities, many of which were present from birth. In the second pedigree there were three cases of detachment with various other ocular abnormalities such as macular lesions, retinal cysts, vitreous veils and dendritic white lines. The results of treatment were very unsatisfactory and even when the detachment could be repaired, central vision remained very poor probably because of a cystic degeneration of the macula. (6 figures, 36 references)

Morris Kaplan.

Linquette, Vouters, and Goudemand. **Is the retinopathy of acute leukemia specific? (Observations on 15 cases.)** *Arch. d'opht.* **12**:699-710, 1953.

The authors have studied 15 cases of acute leukemia and point out the importance of frequent examinations because of the changing ophthalmoscopic picture. They note that the evolution of the retinopathy does not necessarily parallel that of the systemic disease. Certain retinopathies were capable of stabilization or of disappearing completely, and some patients at death showed virtually normal fundi. The authors do not consider the hemorrhages or exudates of the disease as pathognomonic but they do stress the diagnostic importance of the magnitude of the hemorrhages. They believe that while the mechanism of the retinopathy is still undetermined, the hemorrhages should be considered as part of the thrombocytopenic syndrome which is well recognized in acute leukemia. They emphasize the variability of the systemic disease and note that acute leukemia can develop as a manifestation of a predominantly anemic, hemorrhagic, infectious, or leukemic syndrome. (3 tables)

P. Thygeson.

Reimer, L. **The use of hormones as an adjuvant in the treatment of retinal detachments.** *Klin. Monatsbl. f. Augenh.* 122:79-83, 1953.

A 46-year-old castrate had an unsuccessful detachment operation in the first eye. After the operation of the second eye testosterone was given and the retina reattached promptly. (9 references)

Frederick C. Blodi.

Singh, B. P., and Bruce, R. A. **Pregnancy toxemia with bilateral retinal separation.** *Am. J. Obst. and Gynec.* 65:186-188, Jan., 1953.

A case of bilateral separation of the retina is described in toxemia of pregnancy. Recovery after medical treatment was complete. (8 references)

Irwin E. Gaynon.

Smith, T. R., and Pierce, L. H. **Idiopathic detachment of the retina.** *A.M.A. Arch. Ophth.* 49:36-44, Jan., 1953.

In this review of 618 cases of idiopathic retinal detachment certain preoperative factors were found to be significant in altering the prognosis unfavorably. These factors include detachment of the macula, fixed retinal folds, total retinal detachment, multiple breaks in the retina, failure to identify breaks, and aphakia with fixed folds. Other factors were found not to unfavorably influence the prognosis. They are previous extracapsular cataract extraction, lattice-like degeneration, age, and variations in the operative techniques employed. Treatment was successful in from 51 to 57 percent of all cases seen. This figure includes the patients (15 percent) in whom operation was not attempted. Reattachment of the retina for a minimum of six months resulted in 70 to 74 percent of the patients who were operated upon. (14 tables)

George S. Tyner.

Sun, S. F. **Senile disciform degeneration of the macula lutea with report of a case.** *Chinese M. J.* 70:82-86, Jan.-Feb., 1952.

A case of senile disciform degeneration of the macula in the right eye and circinate retinopathy in the left in a Chinese with arteriosclerosis and syphilis of the central nervous system is presented. (2 figures, 11 references)

Irwin E. Gaynon.

12

OPTIC NERVE AND CHIASM

Hsü, Shang-Hsien. **Evulsion of the optic nerve.** *Chinese M. J.* 70:77-81, Jan.-Feb., 1952.

Two cases of traumatic evulsion of the optic nerve are presented. On ophthalmoscopic examination the optic nerve was

absent and was replaced by glial tissue. (2 figures, 14 references)

Irwin E. Gaynon.

13

NEURO-OPHTHALMOLOGY

Abernathy, P. M. **The clinical significance of nystagmus.** North Carolina M. J. 14:73-76, Feb., 1953.

Pendular nystagmus is usually of ocular origin. Jerky nystagmus accompanied by tinnitus and vertigo is of labyrinth origin. Spontaneous nystagmus without vertigo is usually due to a brain lesion. Spontaneous rotatory nystagmus occurs in vestibular nerve and nuclear lesions. Vertical nystagmus is central in origin. Nystagmus without a fast phase indicates a supranuclear lesion. (6 references)

Irwin E. Gaynon.

Cantor, S. J. **A case of congenital dyslexia.** M. J. Australia 1:182, Feb., 1953.

In this case report a youth is described who had visual agnosia, a mental defect, epilepsy and social maladjustment.

Ronald Lowe.

Game, J. **Temporal lobe tumours.** M. J. Australia 1:366-368, March, 1953.

Twenty recent cases are reviewed. Temporal lobe tumors are relatively frequent and often rapidly fatal. They seldom produce symptoms or signs by which they can be recognized with certainty. Uncinate epilepsy occurred in only one fifth of the cases. Field defects were found in 13 out of 17 patients tested, nine had homonymous field defects but only four showed upper quadrantic loss. The majority can be detected by special methods of examination. Associated disturbances of personality and intellect are discussed.

Ronald Lowe.

Parsons-Smith, Gerald. **Ophthalmic**

manifestations of temporal arteritis. Brit. J. Ophth. 36:615-625, Nov., 1952.

Temporal arteritis is an infectious disease of the arteries of the scalp in middle to advanced age, which probably occurs more often than it is recognized; recovery is spontaneous after several months although the affected arteries usually remain obliterated; and the disease is usually benign except as it may affect vision. It is characterized by severe pain and tenderness along the course of the scalp arteries and by fever and malaise. Ocular disturbances occur in about half the patients and may lead to complete loss of vision by causing marked ischemia of the optic nerves. Fifteen cases of temporal arteritis with such ocular lesions as optic atrophy, papilledema, thrombosis of central arteries or veins or their branches, macular hemorrhage, diplopia, ocular pain, ptosis and alexia are described in some detail. The eye disturbances are usually irreversible. There is no satisfactory treatment, but administration of heparin in the fulminant cases might have produced some benefit. (27 references)

Morris Kaplan.

Sunderland, Sydney. **Mechanism responsible for changes in the pupil unaccompanied by disturbances of extraocular muscle function.** Brit. J. Ophth. 36:638-644, Nov., 1952.

Changes in pupillary function often occur which are unaccompanied by changes in function of the other parts of the oculo-motor nerve. An explanation of their origin on purely anatomical grounds is offered. After the nerve leaves the cerebral peduncle and after passing through the lateral sinus it passes through an interval called the tentorial gap which is bounded by the tentorial notch, the dorsum sellae and the brain stem. Here it is intimately related to several important vascular and cerebral structures, disturb-

ances of which can explain the pupillary malfunctions. Above are two branches of the cerebral arteries which pass directly over the nerve while the superior cerebellar artery runs beneath it. A portion of the temporal lobe through which pupillo-constrictor fibers pass is also in intimate contact with the upper part of the nerve. Thus it is seen that anomalous neurovascular relations, aneurysms of any of the vessels, or a herniation of the temporal lobe through the tentorial notch can result in interference with the pupillo-constrictor fibers before functions of the oculo-motor nerve are disturbed. (9 figures, 12 references) Morris Kaplan.

14

EYEBALL, ORBIT, SINUSES

Gensler, H. **Acute exophthalmos.** *Klin. Monatsbl. f. Augenh.* 122:83-86, 1953.

Three elderly patients are described who had acute exophthalmos, which in one was bilateral. All three were in a state of heart failure and a thrombosis of the cavernous sinus was probably the cause of the exophthalmos. (6 references)

Frederick C. Blodi.

Kutscher, Eberhard. **Tuberculosis of the orbital margin.** *Klin. Monatsbl. f. Augenh.* 121:712-715, 1952.

A case of tuberculous periostitis of the orbit was successfully treated with streptomycin. (2 figures, 15 references)

Frederick C. Blodi.

Siedenbiedel, H. **Benign giant cell tumor of the orbit.** *Klin. Monatsbl. f. Augenh.* 122:86-90, 1953.

This benign tumor-like mass was found in the orbit of a 22-year-old man with exophthalmos. This brown tumor stems from bone tissue and presents a localized fibrous osteitis. (5 figures, 14 references)

Frederick C. Blodi.

Stokes, J. J. **Ocular lesions in children**

simulating retinoblastoma: a report of fourteen cases of pseudoglioma. *South. M. J.* 46:63-66, Jan., 1953.

An analysis of pathologic data on 14 eyes which were removed because of suspected retinoblastoma is reported. In 11 of these 14 eyes the lesions were post-inflammatory exudative retinitis (Coats'). This incidence agrees closely with that of the series reported by Sanders and indicates the conditions most often mistaken for retinoblastoma.

Theodore M. Shapira.

15

EYELIDS, LACRIMAL APPARATUS

Allen, James H. **Lids, lacrimal apparatus, and conjunctiva.** *A.M.A. Arch. Ophth.* 49:90-109, Jan., 1953.

Allen reviews 180 pertinent articles in the recent literature in 19 pages. (190 references)

George S. Tyner.

Boase, A. J. **Tarsectomy.** *Brit. J. Ophth.* 36:645-648, Nov., 1952.

In East Africa trachoma abounds and trichiasis-entropion is very common and very disabling. The operation for its relief which is described is done by the author at the rate of 2,000 annually. It consists of a simple tarsectomy and can be accomplished in 7 to 10 minutes. The lid is infiltrated with procaine-adrenalin and then everted with a Cruickshank forceps; the tarsus is incised from canthus to canthus in the subtarsal sulcus and is removed by a second incision through the conjunctiva at the upper end of the plate. The conjunctiva is sutured by a mattress suture of catgut going out through the skin and the eye is bandaged for 24 hours. The operation is uniformly successful with little reaction and is highly recommended for all cases of entropion. (5 figures)

Morris Kaplan.

Greeves, Affleck. **Streptothrix conjunctivitis.** *Brit. J. Ophth.* 36:653, Nov., 1952.

Normally streptothrix infestation is limited to one or both canaliculi with very little irritation of the surrounding conjunctiva. Two cases of long-standing, resistant conjunctivitis which healed promptly after the monilia were found in the canaliculi and evacuated are briefly described.

Morris Kaplan.

Marin Amat. **Permanent drain during the postoperative course of a dacryocystorhinostomy, and especially of a dacryorhinostomy.** Arch. Soc. oftal. hispano-am. 12:1335-1339, Nov., 1953.

To prevent occlusion of the anastomosis between the lacrimal sac and the nose, Marin Amat uses a horse-hair suture as a drain. After the surgical field is exposed and the transosseous opening into the nose made, the suture is passed through the inferior canaliculus and the surgical field into the nose, and out through the nasal vestibule. The two ends of the thread are fixed on the face. The drain is maintained in the lacrimal passages for eight days. (3 figures, 5 references)

Ray K. Daily.

Meyer, F. W., and Kluth, C. **The cause of bloody tears.** Klin. Monatsbl. f. Augenh. 121:719-724, 1952.

The author saw two cases, one caused by a capillary hemangioma of the conjunctiva, the other one probably a case of hysteria. Other causes of bloody tears can be disease of the conjunctiva or the lacrimal gland, menstruation, mechanical irritation, and acetylcholine. (2 figures, 52 references)

Frederick C. Blodi.

Smith, B., and Pang, H. G. **Blepharoptosis treated by the Friedenwald-Guyton suture.** A.M.A. Arch. Ophth. 49:45-48, Jan., 1953.

The technique for correcting blepharoptosis with the Friedenwald-Guyton suture is described. 35 patients were treated by this method and successful re-

sults were obtained in 83 percent. This method is indicated 1. when other procedures have failed, 2. to avoid exposure keratitis, 3. when there is undetermined levator or superior rectus function, or 4. acquired paralytic ptosis, 5. as a temporary procedure, 6. in patients with a Marcus-Gunn syndrome, and 7. as a procedure for inexperienced surgeons. (1 figure, 6 references)

George S. Tyner.

16

TUMORS

Cronin, T. D. **Extensive pigmented nevi in hairbearing areas: removal of pigmented layer while preserving the hair follicles.** Plast. & Reconstruct. Surg. 11: 94-106, Feb., 1953.

The usual methods of removal of extensive pigmented nevi of the scalp or eyebrow result in a bald spot or loss of the eyebrow. Reparative procedures usually require multiple stages and the final result is likely to be something less than normal. Since the pigment and nevus cells are in the upper half of the dermis and the hair follicles are in the lower half of the dermis and subcutaneous tissues, the author removes the former, as in taking a split skin graft, and thus preserves the hair follicles and the capacity to grow hair. The author uses this method without fear of malignant change in intra-dermal nevi at any age, but in the case of junctional or compound nevi, he restricts its use to children below the age of puberty. His results have been so satisfactory that he now uses it on extensive non-hairy nevi in non-hairbearing areas, but he does not recommend this method for small nevi where simple full-thickness excision is best.

Alston Callahan.

De Unanimo, R. **Dermoids of the sclero-corneal limbus.** Arch. Soc. oftal. hispano-am. 12:1291-1297, Nov., 1952

A dermoid of the limbus was excised

from the left eye of a patient, 17 years old. She returned four weeks later with a granuloma at the site of the tumor. Removal of the granuloma was followed by a permanent cure. To avoid the development of granulomas, the author suggests that after a clean excision of the tumor from the corneal tissue by parallel cuts of the knife, as in a keratotomy, the wound should be covered with a conjunctival flap and fixed to the limbus by three scleroconjunctival sutures. The literature on dermoids of the eyeball is reviewed. (10 figures, 20 references) Ray K. Daily.

18

SYSTEMIC DISEASE AND PARASITES

Franceschetti, A., Blum, J. D., and Bamatter, F. **Diagnostic value of ocular symptoms in juvenile chronic polyarthritides (Still's disease).** Tr. Ophth. Soc. U. Kingdom 71:17-26, 1951.

In 1896 George Still separated from the mass of articular diseases of childhood a classical syndrome consisting of chronic periarticular polyarthritides which progresses with variable periods of remission without much damage to the bone itself, and is accompanied by generalized enlargement of the lymph glands and splenomegaly. The arthritis, although affecting many joints, is benign and transient in character. A raised blood sedimentation rate may be the only indication of a rheumatoid affection. The ocular lesions consist of a slow chronic iridocyclitis, an early band-shaped degeneration of the cornea, and a complicated cataract. The appearance of chronic iridocyclitis in a child should make one think of Still's disease because iridocyclitis is rare in childhood. In the 14 histories reviewed, the iridocyclitis appeared between the ages of two and 14 years. The ocular lesions may precede or follow the joint disease. The iridocyclitis is usually bilateral and remained unilateral in only 5 of the 14 patients presented. Many of the eyes de-

velop phthisis bulbi or secondary glaucoma. Parkinsonian type of facies with its characteristic masklike expressionlessness is frequent. Typical osteoporosis with integrity of the articular margin easily differentiates Still's disease from a tuberculous lesion.

During the acute phase a periarticular swelling with rubbery consistency is characteristic. (8 figures, 11 references)

Beulah Cushman.

Muscas, M. **Two unusual cases of hemorrhagic meningitis after injury to the orbit.** Boll. d'ocul. 31:703-706, Nov., 1952.

The author could find no reference in the literature to hemorrhagic meningitis after orbital trauma. A 14-year-old girl developed hemorrhagic meningitis from a knife wound, 1½ cm. long, in the lower outer quadrant of the orbit. Culture of the cerebrospinal fluid showed no growth; the Pandy reaction was slightly positive. The cerebrospinal fluid remained sanguinous for a few days; the patient recovered with one normal eye and one retaining only light perception.

A 36-year-old woman was hit by a piece of wood which entered the right orbit penetrating three centimeters. Typical meningitis developed, the cerebrospinal fluid contained blood, and cultures were negative. After six weeks under sulfonamide treatment the patient recovered. (6 references) K. W. Ascher.

Nutt, A. B. **The association of ocular and articular disease.** Tr. Ophth. Soc. U. Kingdom 71:149-160, 1951.

The author discusses the association of eye lesions with the mucocutaneous syndromes and the diffuse collagen diseases.

Five diseases are characterized by lesions involving the eyes, mouth, genitals and in many cases the joints. They are described as pluriorificial erosive ectodermosis, Baader's dermatostomatitis, Stevens-Johnson's disease, Behçet's disease and

Reiter's disease. The diffuse collagen diseases are characterized by widespread alterations in the connective tissue, particularly by abnormalities of its extra-cellular components as in rheumatic fever, rheumatoid arthritis, polyarteritis nodosa and acute disseminated lupus erythematosus. Fibrinoid degeneration of the collagen fibers and myxomatous swelling of the ground substance are an indication that certain chemical and physicochemical changes take place in the tissues. The idea of tissue disease accounts for the diversity of clinical manifestations in these diseases. Sjögren's syndrome in late rheumatoid arthritis shows the eye symptoms of diminished tear secretion with changes in the cornea and conjunctiva. Scleromalacia perforans is a rare condition in which holes occur in the sclera without the usual signs of inflammation. Spondylarthritis occurs most frequently in men and may give the clue to the existing pathogenesis of iritis if gonococcal infection is ruled out. Chronic polyarthritis in children, chiefly girls, may be associated with ocular signs. The symptoms typical of Still's disease include enlargement of the lymphatic glands and spleen. The ocular changes comprise insidious iridocyclitis, band degeneration of the cornea, and slight impairment of the deeper parts of the eye. The ophthalmoscopic signs of polyarteritis nodosa are blurring of the disc, juxtapapillary hemorrhages, areas of retinal edema, transient retinal detachment, tubercle-like nodules of choroiditis which heal leaving lightly pigmented scars, and arteritis affecting the retinal arteries, followed by obstruction of the lumen, aneurysmal dilatation and scar formation. Malignant lupus erythematosus may be associated with certain eye changes such as edema of the disc, retinal hemorrhages, cotton wool patches, detachment of the retina and optic atrophy. (43 references)

Beulah Cushman.

Rieger, H. **Cases with non-corresponding toxoplasma tests.** Wien. klin. Wchnschr. 64:945-947, Dec., 1952.

In infection with toxoplasma, a correspondence of the skin test after Frenkel and the serum color test after Sabin-Feldman is found in the majority of cases. In 18 percent of the author's patients whose eyes were infected with toxoplasma either the skin test or the blood titer test was negative. It is the author's opinion that these differences are not due to laboratory errors. He reasons that the antibodies in the blood do not develop at the same time as skin sensitivity becomes evident. Antibodies may also disappear from the blood before the skin loses its specific allergic sensitivity. These differences give a theoretical explanation for noncorresponding toxoplasma tests. (1 figure, 12 references)

Max Hirschfelder.

Rieger, H. **Ocular toxoplasmosis and hepatitis epidemica.** Deutsche med. Wchnschr. 77:1250-1252, Oct., 1952.

The author observed three patients with retinopathy due to toxoplasmosis, which was preceded or followed by epidemic hepatitis. In one family a patient with intermittent hepatitis was found who had a positive toxoplasma reaction. It is possible that patients with toxoplasmosis show an increased disposition to epidemic hepatitis. One must also consider the possibility that toxoplasmosis is the cause of this type of hepatitis, even though the literature is vague on this subject. It is suggested that all patients with epidemic hepatitis be tested for reaction to toxoplasma.

Max Hirschfelder.

Saenz Canales, José. **Present day problem of ocular cysticercosis.** An. Soc. mex. de oftal. 24:30-52, Jan.-March, 1950.

Vosgien found that 47 percent of cysticercus infestation affected the eye. The most common species is *Cysticercus cellulosae*. The infestation could be attained

by either a heteroinfestation, internal autoinfestation or external autoinfestation. In the eye it is found extraocularly or intraocularly. The most common site is subretinal, then intravitreal and then subconjunctival. It has been found to a lesser degree in the anterior chamber, in the orbit, iris, choroid and Tenon's capsule. The parasite reaches these structures by way of their blood supply. The early diagnosis of intraocular cysticercosis depends on the visual symptoms. In the vitreous the cyst can be seen to have a diversity of movements. When the vitreous is clear the diagnosis may be relatively easy but when opacification starts it may be very difficult. The parasite may cause uveitis, secondary glaucoma, degeneration of the globe and phthisis bulbi. Various techniques of extracting the vesicle from the globe are discussed. The prognosis is grave even after a successful removal from the globe. Other aids in the diagnosis are blood studies for eosinophilia, skin test and complement fixation. (76 references)

Jose Pietri.

Siboni, D. **A case of ocular miosis due to rhinoestrus.** Ann. d'ocul. 185:966-969, Nov., 1952.

A boy who had been struck in the face with mud developed an acute inflammation of the lids and conjunctiva in the right eye one week later. Six white foreign bodies, each about 1.5 mm. long, were removed from the upper cul-de-sac and identified as oestrus ovis larvae. Healing promptly followed.

Chas. A. Bahn.

Silvan, F. **Migrating subcutaneous parasite, with temporary invasion of the orbit.** Arch. Soc. oftal. hispano-am. 12: 1189-1195, Oct., 1952.

The literature is reviewed and a report of a case of a hypodermic myiasis is de-

scribed, in which the parasite entered the face through the wound, and in the course of its migrations remained for a time in the orbit. The patient, a child six years old, was struck a blow with an ear of corn, which produced a lacerated contusion on the side of the nose in the region of the lacrimal sac. Several days later the child developed swelling of the lids, with some exophthalmos, and complained of intermittent pain in the lids and orbit. The larva of the parasite probably entered the orbit through the small abrasion in the skin. The parasite migrated from the orbit to the temporal region, then down over the cheek, neck, and shoulder and finally after seven months burrowed an exit through the skin in the axilla, through which it was removed. The emigration of the parasite from the orbit was promoted by the application of hot compresses. This leads the author to suggest that diathermy may be used to drive the parasite to an accessible region, where it may be destroyed by a 30 seconds long application of ethyl chloride. (7 figures, 7 references)

Ray K. Daily.

Stankiewicz, Remigiusz. **Scrofula in children a benign form of tuberculosis.** Klinika Oczna 22:225-234, 1952.

Ninety-five percent of scrofulous children have positive skin reaction to tuberculin. Frequently there are signs of inactive pulmonary lesions or active extrapulmonary tuberculosis. The author examined 74 children from 7 months to 10 years of age. Their symptoms were blepharo-conjunctivitis, follicular conjunctivitis, dermatitis of the lids and lips, and cervical lymphadenitis. In 80 cases of tuberculous meningitis in children seen by the author, examination and history did not reveal any signs of scrofula. (2 figures, 11 references)

Sylvan Brandon.

NEWS ITEMS

Edited by Donald J. Lyle, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received at least three months before the date of occurrence.

DEATHS

Dr. William Carle Davis, Columbus, Ohio, died March 8, 1953, aged 78 years.

Dr. Clyde Percy Dyer, St. Louis, Missouri, died February 19, 1953, aged 68 years.

Dr. John Silliman Macnie, Minneapolis, Minnesota, died January 30, 1953, aged 78 years.

ANNOUNCEMENTS

COLORADO MEETING

The summer convention of the Colorado Ophthalmological Society will be held on August 3, 4, 5, and 6, 1953, in conjunction with the Department of Graduate Education of the University of Colorado Medical School. Guest speakers, seminars, and demonstrations will constitute the four-day meeting, to be held at the University of Colorado Medical Center in Denver. Membership in the society and attendance at the meeting are open to all interested and accredited physicians. For information on registration and fees, write to the Director of Graduate Education, University of Colorado Medical School, 4200 East 9th Avenue, Denver, Colorado.

MISCELLANEOUS

RIO DE JANEIRO COURSE

Recently the Department of Clinical Ophthalmology of the School of Graduate Medicine, Polyclinic Hospital, Rio de Janeiro, under the direction of Dr. Pedro Moacyr de Aguiar, gave two postgraduate courses, the first on ocular motility and the second on orthoptics.

GILL MEMORIAL HOSPITAL COURSE

The Gill Memorial Eye, Ear, and Throat Hospital, Roanoke, Virginia, has just completed the 26th annual refresher course in ophthalmology and otolaryngology. There were about 300 doctors in attendance and 45 states, Canada, and several foreign countries were represented.

The 27th annual spring congress will be held from April 5 to April 10, 1954.

GOLDEN JUBILEE

To celebrate its golden jubilee, the Ophthalmological Society of Egypt, with the collaboration of the regional office of the World Health Organization, organized scientific meetings that lasted for two weeks. Prof. Karl D. Lindner, Vienna; Dr. Philips Thygeson, San Jose, California; Prof. Rudolf Thiel, Frankfurt am Main; Dr. T. Kieth

Lyle, London; Prof. H. N. H. Ehlers, Copenhagen; and Dr. David G. Cogan, Boston, were invited by the regional office to attend the ceremonies, deliver lectures, perform operations, and attend discussion groups.

The ceremonies were opened by a formal address given by Dr. Nour El Din Tarraf, minister of Public Health. This was followed by addresses by Dr. Ali Tewfik Shausha, director of the Regional Health Bureau of the East Mediterranean, and by Dr. Mohammad Tewfik, president of the society. Professor Lindner started the scientific meetings by delivering the Soliman Lecture on "Improvement or cure of myopia by one- or two-stage scleral resection."

During the first three days, lectures and papers were read by the six visitors, by the members of the society, and by guests from Europe and from the Near and Far East. On the fourth day an ophthalmic seminar was begun. The daily program of the seminar ran as follows: Operations from 9 to 11 a.m.; a clinical conference from 11 a.m. to 1 p.m.; a lecture from 3:30 to 4:15 p.m.; a discussion group from 4:30 to 5:45 p.m., and a film lecture from 5:45 to 6:30 p.m.

The operations were done in four theaters, two at Fouad 1st Hospital, one at Demerdache Hospital, and the fourth at Giza Ophthalmic Hospital. The four operators, Professor Lindner, Dr. Lyle, Professor Thiel, and Professor Ehlers, made the round of all the four theaters. The operations performed comprised cataract extractions, glaucoma operations, dacryocystorhinostomy, scleral resection for retinal detachment and for high myopia, Sato's operation for keratoconus, and operations for squint.

The following lectures were delivered by the six guest speakers during the ceremonies:

Professor Lindner: "Improvement or cure of myopia by one- or two-stage scleral resection," "The etiology of myopia," and "The pathology of the vitreous."

Dr. Thygeson: "Observations on the use of cortisone and hydrocortisone in ophthalmology," "The follicular conjunctivitis," and "The ocular manifestations of the major dermatoses."

Dr. Lyle: "The operation of dacryocystorhinostomy and its modification when the lacrimal sac is fibrotic or has already been removed," "The treatment of concomitant strabismus in children," and "Ocular palsy of congenital origin and its treatment."

Professor Thiel: "Diagnostic significance of fundus changes in hypertension," and "Differential diagnosis and treatment of chronic uveitis."

Dr. Cogan: "Radiation effects on the eye," "Corneal physiology," and "Film lectures on many syndromes."

Professor Ehlers: "The proliferating diabetic retinopathy," "The clinical evaluation of visual acuity," and "Horner's syndrome."

At the business meeting held on the first day of the ceremonies, the following officers and members were elected to form the council of the society for 1953: Dr. Ahmad Kamel, president; Dr. Mohammad Osman Yousef, vice-president; Dr. Ibrahim Ahmad Mohammad, honorary treasurer and archivist; Dr. Sabri Kamel, honorary secretary; Dr. Mohammad Tewfik Ismail, honorary assistant secretary; Dr. Ibrahim Ahmad Abboud, Dr. Ismail Disouki, Dr. Anwar El Masry, and Dr. Hanna Salib Ghobrial, members.

SOCIETIES

READING MEETING

The guest speaker at the 134th meeting of the Reading (Pennsylvania) Eye, Ear, Nose, and Throat Society was Paul Boeder, Ph.D., instructor in ophthalmology at the Harvard Medical School, and director of the Bureau of Visual Science at the American Optical Company, Southbridge, Massachusetts. The subject of his address was "Some aspects of optics."

A study club was conducted on the subject of "Lighting problems in industry and in the school." Instructors were: Mr. Frederick R. Shenk, Wyoming, an architect, and Mr. H. B. Elliott, West Reading, an illuminating engineer.

The following officers were elected to serve for the 1953-54 term: president, Dr. M. K. Rothernberger, Allentown; vice-president and president-elect, Dr. Paul C. Craig, Reading; secretary, Dr. James H. Parker, Jr., Reading; treasurer, Dr. Philip R. Wiest, Reading.

UNITED KINGDOM PROGRAM

At the recent annual congress of the Ophthalmological Society of the United Kingdom held

at the Royal Society of Medicine, London, the following program was presented:

Address of the president, Dr. A. MacRae, "Prognosis in malignant melanoma of choroid and ciliary body." "Keratoconus associated with thyrotoxicosis" was read by Mr. E. F. King; "A bulbar pressure test for glaucoma," Mr. P. L. Baxter; "Individuality in ophthalmology," Mr. A. G. Cross; "The course of thrombosis of the retinal veins," Mr. Arthur Lister and Mr. F. B. Zwink; "Clinical survey of 600 N.H.S. contact lens cases," Mr. Frederick Ridley; "Some pitfalls in the diagnosis of plerocephalic edema," Mr. T. Keith Lyle; "The Stevens-Johnson syndrome," Mr. A. L. McCurry; "Corneal calcification," Mr. J. H. Daggart.

Professor Sir Geoffrey Jefferson presented the Bowman Lecture, the subject of his address being "The syndromes of the cavernous sinus." "Changes in the refraction of the eye following the operation of lamellar scleral resection" was given by Mr. C. Dee Shapland; "Some aspects of total color blindness," Mr. R. A. Weale; "Vascular patterns on the eye," Mr. F. R. Neubert; "A simple applanation tonometer," Mr. E. S. Perkins; "Topical cortisone," Dr. Alexander E. MacDonald.

Professor Robert Cruickshank, Professor Arnold Sorsby, and Mr. Derek Ainslie were openers for the discussion on "The scope of antibiotics and chemotherapeutic agents in ophthalmology." Films were shown on the following subjects: "Intracapsular extraction" and "Insertion of a plastic lens," Mr. A. S. Philips; "Certain details of iridencleisis," Professor G. P. Sourdille; "Lamellar scleral resection," Mr. C. Dee Shapland; "The intraocular acrylic lens operation," Mr. Harold Ridley.

PERSONALS

Dr. William M. Hart, assistant professor of ophthalmology of Jefferson Medical College, Philadelphia, Pennsylvania, has been appointed Chief of the Ophthalmology Clinics of the National Institute of Neurological Diseases and Blindness, Public Health Service. His appointment began as of April 15th.

Dr. Arthur J. Bedell, Albany, New York, recently returned from a lecture tour in Johannesburg, Cape Town, and Cairo, and Athens, Greece.

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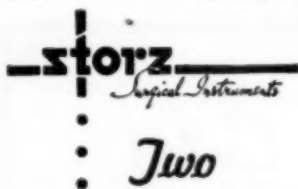
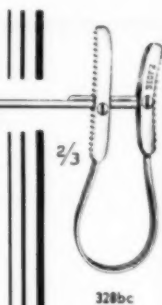
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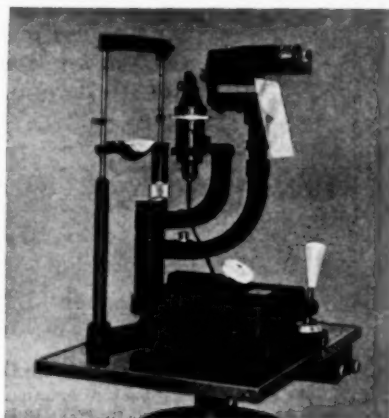
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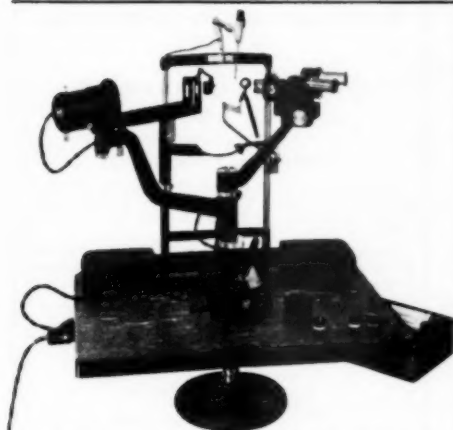
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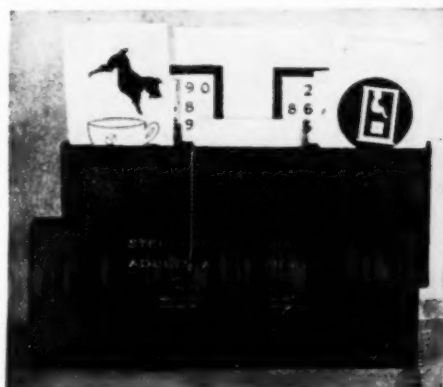
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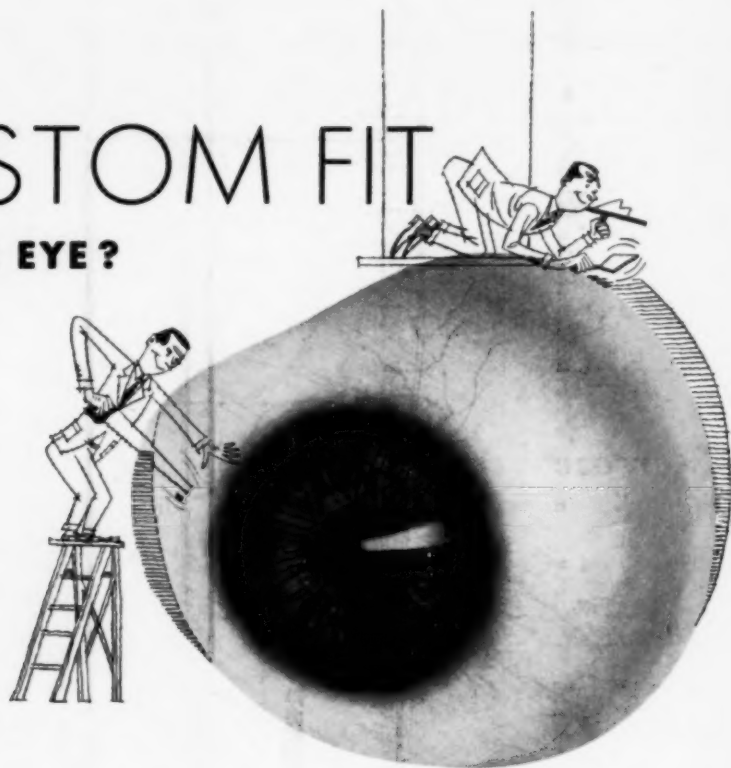
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Funds for the establishment of the Research Medal of the Association for Research in Ophthalmology were donated in 1947 by Mrs. Francis I. Proctor of Santa Fe, New Mexico, as a memorial to her late husband. Dr. Proctor, a Boston ophthalmologist, became intensely interested in the experimental side of ophthalmology after his retirement, and participated in numerous studies on the etiology and treatment of trachoma. The purpose of the medal is to stimulate research and to honor investigators who have made notable contributions in the basic fields of ophthalmology. The medal is to be awarded without regard to the nationality or professional status of the recipient.



V. EVERETT KINSEY, PH.D.

BIOGRAPHICAL DATA

V. EVERETT KINSEY, PH.D.

V. Everett Kinsey was born in Pittsburgh, Pennsylvania, in 1909. He received a B.S. degree at the University of Pittsburgh in 1931, and in 1932 he assisted Dr. Nicholas Rashevsky in biophysical research at the Research Laboratory of the Westinghouse Electric Company in East Pittsburgh. Dr. Kinsey obtained a Ph.D. degree in zoology at the University of Pittsburgh in 1935 where he conducted studies on the biologic effects of X rays.

The following year he continued his research on the effects of short-wave radiations at the Cancer Research Laboratory at the University of Pennsylvania in Philadelphia and, during 1937 and 1938, he worked as a research biochemist at the Mulford Biological Laboratory of the Sharp and Dohme Company in Philadelphia where he investigated improved methods for purification of antitoxins.

From 1938 to 1940, he was an associate in research in ophthalmology at the School of Medicine of the University of Pittsburgh. In 1940, he joined the staff of the Howe Laboratory of Ophthalmology of the Harvard Medical School as an assistant in ophthalmic research. He later held the position of associ-

ate, instructor, and assistant professor of ophthalmic research, and from 1946 through 1950 he was also director of research on retrolental fibroplasia at the Massachusetts Eye and Ear Infirmary in Boston.

In 1950, Dr. Kinsey became assistant director of research at the Kresge Eye Institute in Detroit and was appointed professor of ophthalmic chemistry at the Wayne University College of Medicine.

Dr. Kinsey is an honorary member of the New England Ophthalmological Society, a special member of the Detroit Ophthalmological Society, a member of the Detroit Physiological Society, the Association for Research in Ophthalmology, the American Chemical Society, and Sigma Xi. He is chairman of the Scientific Advisory Board of the National Foundation for Eye Research, a member of the executive committee on research of the National Society for the Prevention of Blindness, an associate editor of the *Archives of Ophthalmology*, and a member of the Sensory Diseases Study Section of the U. S. Public Health Service. Dr. Kinsey was co-winner of the Warren Triennial Prize of the Massachusetts General Hospital in Boston in 1944.

PUBLICATIONS BY V. EVERETT KINSEY, PH.D.

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REMARKS MADE ON ACCEPTANCE OF THE PROCTOR MEDAL AWARD

June, 1952

V. EVERETT KINSEY, PH.D.

Detroit, Michigan

It was Shakespeare, I believe, who in speaking of the quality of mercy said that "it is twice blessed." I feel that way this evening for I have had the joy of sharing in the performance of the research for which this medal is given, and at the same time have the pleasure of receiving it. I am deeply appreciative, and accept the Proctor Medal Award realizing that it is given for investigations pursued not by myself alone, but by a number of outstanding collaborators and assistants.

The environment which influenced the course of my career in ophthalmic research was, and is, one in which collaborative research comes quite naturally.

When Dr. David Cogan became director of the Howe Laboratory of Ophthalmology in 1940, upon Dr. Frederick Verhoeff's retirement, he recognized that ophthalmic research had progressed to a point beyond that described by Dr. Jonas Friedenwald several years ago as the natural history or classification phase of science.

In this more mature phase of ophthalmic research Dr. Cogan believed that continued progress would depend more and more upon utilization of the combined talents of individuals having varied backgrounds and interests. And so he set out to bring individuals trained in the basic sciences into the ophthalmic field, and, as he said, in effect, encourage them to apply their talents co-

operatively in a laboratory, closely associated with a clinic, where collaboration with clinicians would be mutually beneficial.

Having already become interested in ophthalmic problems through my association and work on the effects of infrared radiation on the eye with the late Dr. Charles Kutscher of Pittsburgh, I was enthusiastic about entering into such a cooperative and pioneering venture. That my future, in what was then regarded as almost exclusively a clinical field, would be anything but black was not at all apparent to my colleagues in basic sciences, and that a basic scientist could contribute anything to such a clinical field must have been equally doubtful to some, when I recall that one of the members of the staff of the Massachusetts Eye and Ear Infirmary, who incidentally left Boston long ago, questioned the judgment, if not sanity, of Dr. Cogan when he hired, and worse still, allocated space to "a man who was not even an ophthalmologist." I was not alone, however, as Dr. Elek Ludvigh, who, as you know, is a biophysicist, had been associated with Dr. Verhoeff in the Howe Laboratory for a number of years. It was in this stimulating milieu that I arrived in 1940, where, by design, emphasis was to be placed on the collaborative type of research.

The men whose efforts and talents contributed to the studies with which we are concerned this evening are familiar to most

of you. First, Dr. Cogan's broad clinical experience and knowledge of the eye, plus his ability to place his finger on the weak spot in an experiment or suggest a different approach to a problem, were exceedingly helpful to me. Our studies on the permeability and turgescence properties of the cornea offered an opportunity to learn the value of collaborative research.

Dr. Morton Grant's industry and insight contributed to the early studies of intraocular-fluid dynamics and to the long series of investigations on the biologic effects of war gases which we pursued throughout the war years. The boundless energy and originality of approach of Dr. Ernst Bárány, of Uppsala, Sweden, made possible the measurements of the rate of flow of aqueous humor, and interpretation of much data on the physiology of intraocular fluids.

The interpretation of much of the research has depended upon quantitative relationships, the mathematical expression of which, in large part, is attributable to the unique ability of Dr. Ludvigh to translate biologic concepts into mathematical equations. The technical skill of Dr. Frederic Merriam made possible the development of techniques for culturing the lens in a manner which permits the quantitative study of its metabolism.

The personal enthusiasm of the late Dr. Theodore Terry and his extraordinary interest in retrolental fibroplasia influenced me to continue study of this disease after his death. Dr. Blanche Jackson, Dr. Martin Williamson, Dr. Leona Zacharias, and Dr. Paul Goldhaber contributed greatly to the basic aspects of this research, and the clinical studies would not have been possible without the help of Dr. Julian Chisholm and Dr. Merrill King.

At the Kresge Eye Institute in Detroit, Dr. Charles Frohman, with his intimate knowledge of intermediate metabolism, has made it possible to study some of the more subtle aspects of the chemistry of the lens. In this new location I receive the continued benefit of Dr. Ludvigh's brilliant analytical

mind plus the astute clinical counsel of Dr. Albert Ruedemann.

It is abundantly evident that the work for which the Proctor Award is given has been the result of conjoint effort, and it is for illustration of this point that I have drawn so heavily on my personal experience. Previous recipients of this award have likewise pointed to the collaborative nature of their research and stressed its benefits. Collaborative research, however, is possible only in the midst of collaborators, and, in the past, few institutions could afford even a nucleus of research workers.

We are now in the midst of an economic revolution so far as financial support for research in ophthalmology is concerned—a revolution which might be expected to improve both the quantity and quality of basic research in ophthalmology. This seems to be a fitting time to discuss briefly some of the changing economics of research in this field and to point to several factors which I feel must be taken into account if ophthalmology is to profit maximally from additional financial support.

Increased funds for research first became available in relatively large amounts during the last war from both the Armed Services and the Office of Scientific Research and Development. Because of the unsettled international situation, postwar funds for more or less assigned studies have continued to be made available by the Army and Navy and also by the Veterans Administration.

During the past three years investigations concerned with radiation cataracts have received relatively large support from the Atomic Energy Commission. But governmental support which promises to be largest in amount and influence to the greatest extent the course of research in ophthalmology will come from the new Institute for Neurological Diseases and Blindness of the U. S. Public Health Service.

The amount allocated for eye research from all governmental agencies amounted to

about \$700,000 for the years 1950 and 1951.* This sum represents an increase of approximately fivefold in governmental aid of research compared with the years 1946, 1947, and 1948, and, roughly speaking, doubles the total funds available for ophthalmic research.

The amount of money from private sources has increased too. Funds from the Kresge Foundation, for instance, made it possible to establish the Kresge Eye Institute in Detroit, and grants from this foundation have been given to ophthalmic investigators in other communities. The Proctor and Doheny funds have aided research workers on the West Coast in pursuing their ocular investigations on an expanded scale.

Sums contributed by individuals, who usually are interested in a specific disease, have enabled some investigators in various parts of the country to augment their research activities. Unfortunately, private funds have not increased to the extent of governmental funds. While a comparison of the amount of money currently allocated for research in ophthalmology with that of even a few years ago may be misleading because of higher costs, the fact remains that more money is available now than ever before.

With the exception of a part of the funds from private sources, the increased money available for basic research in ophthalmology has been given almost exclusively for the support of projects on a short-term basis. By and large this kind of financing, even though some of the grants are subject to renewal, only makes it possible for established investigators to hire assistants and to obtain additional laboratory equipment. It does not permit appreciable expansion of the basic framework on which the national effort in basic research in ophthalmology rests.

It seems to me that unless we are to become top-heavy with short-term projects pursued by the relatively few individuals who at present conduct most of the basic

research in ophthalmology in the country, it is necessary that provision be made to enlarge this basic framework.

Believing as I do in the advantages of collaborative research which in this field frequently involves the full-time investigator, enlargement can best be accomplished, I think, by establishing for the career investigators more permanent positions—positions which at the top level should carry with them tenure and academic rank corresponding to the full professorships which until two years ago were available only in clinical ophthalmology.

How else can we attract the best qualified men from the basic-science field or expect a clinically trained ophthalmologist with a desire to do research to forego the financial and sometimes even academic rewards of private practice?

More laboratory space for experimental studies is another requisite. The present facilities in most of the institutions with which I am familiar are already overcrowded. This space should be in proximity to the clinic, not only to speed practical application of laboratory observations but to maintain close contact with the clinician.

The number of pages of ophthalmic journals and amount of time at meetings devoted to the dissemination of knowledge in basic ophthalmic research may have to be increased as augmented research efforts lead to an increase in the papers requiring more or less immediate presentation. A partial solution to this problem, incurring no financial burden, may be to employ the method of referees used by some of the journals and societies in the basic scientific fields. This suggested solution to the problem has the added advantage of maintaining quality.

These three requirements, personnel, space, and facilities for presenting experimental data, must be adequately fulfilled if we are to provide a sound basis for expansion of the over-all framework of basic research in ophthalmology. They all demand long-term planning and long-term planning

* Deignan, S. L., and Miller, E.: The support of research in medical and allied fields for the period 1946 through 1951. *Science*, 115:321, 1952.

is valueless without long-term grants.

It is my belief that we who are most concerned with the future of basic ophthalmic research should continue to emphasize this point to private and governmental agencies which have brought about the economic revolution in ophthalmic research. Only by being vocal can we make certain that a greater proportion of the grants will be

made available for periods long enough to establish research organizations having sufficient permanence to assure acquisition of a staff of high caliber.

Again I wish to express my appreciation to the members of this society for the honor bestowed upon me.

690 Mullett Street (26).

THE DEVELOPMENT OF THE EXTRINSIC MUSCLES OF THE EYE

WALTER H. FINK, M.D.

Minneapolis, Minnesota

A study of the developmental anatomy of the extrinsic muscles is of interest to both the anatomist and the clinician.

The anatomist's interest centers on a background which makes possible that mature anatomic picture; the clinician's interest centers on a background of anatomic facts which assist him in understanding the normal and abnormal actions of the extrinsic muscles, thus making possible the diagnosis of an obscure clinical problem.

A review of the available data concerning the development of the extrinsic muscles reveals a very incomplete picture. Although an appreciable amount of information is available during this period concerning other phases of ocular development, little attention has been directed to the development of the extrinsic muscles. Most of the references to the extrinsic-muscle development pertain to lower vertebrates and deal only with the very early embryonic period of development. Gilbert's¹ monumental work, which has just been completed, has added appreciably to our knowledge of the very early embryonic extrinsic muscle development in man.

Because of the state of uncertainty which exists concerning the later development of the extrinsic muscles, it seems advisable to assemble various pertinent facts concerning this phase of their development, some of

which are known and some of which have been determined in a study that I made of a series of specimens. The present study begins where Gilbert's study (early embryologic period) stopped and carries the development to maturity, thus completing the entire period of development of the extrinsic muscles in man.

The presentation is based upon a study of a series of human specimens in which the successive stages of development of the extrinsic muscles are noted. The specimens studied cover the period from the 40-mm. stage to maturity.

It must be recognized that such a presentation is not all inclusive but rather a step toward the completed picture and many wide gaps in our knowledge concerning extrinsic muscle development will remain. It is hoped, however, that this study will assist in clarifying some of the more obscure phases of extrinsic-muscle development and act as a stimulant to further study in this field.

A study of this nature involves not only the developmental process of the extrinsic muscles but also a background of knowledge concerning their comparative development. Such a background enables us to appreciate the basis for the various developmental processes.

In this presentation the various aspects of

extrinsic muscle development will be considered in the following categories:

A. Developmental factors related to the extrinsic muscles as a whole.

B. Developmental factors related to the origin and insertion of the extrinsic muscles.

C. Developmental factors related to the position of the eyeball.

A. DEVELOPMENTAL FACTORS RELATED TO THE MUSCLES AS A WHOLE

In studying the development of the extrinsic muscles of man, certain facts become evident:

1. Available evidence indicates that the initial development of the extrinsic muscles in man is similar to that of other higher vertebrates.

In his recent work on the early development of the extrinsic muscles of the human embryo, Gilbert¹ has given definite proof that in the higher mammals, the mass of mesoderm from which the eye muscles are developed should be regarded as representing the fusion of persisting parts of three of the most rostrally located of the head somites of primitive ancestral forms. This interpretation is supported by the fact that the innervation of the eye muscles is of the same character as that of muscles of somitic origin in other parts of the body.

The knowledge of a similarity in the pattern of development in lower forms and in man gives us a better basis for the appreciation of the highly complicated development as found in man.

2. The extrinsic-muscle development in man occupies a high position in the scale of phylogenetic development. The fundamental factor which seems to govern the degree and type of extrinsic muscle development is environment. One of the most striking features of the influence of environment is the variable degree and type of muscle development found in passing from the simpler forms of life upward through the various levels.

The invertebrate eye not only shows more

primitive extrinsic muscle development than the vertebrate eye, but also a wide variation in type due to environmental influences.

At the vertebrate level, there is a constant and complicated system of muscles, consisting usually of four recti, two obliques, and, in the majority of cases, a retractor. Despite this complicated apparatus and its efficient nerve supply, the eyes of fishes, reptiles, amphibians, birds, and aquatic mammals show wide variations in type of extrinsic muscle development, largely owing to environmental conditions.

The relative importance of the individual extrinsic muscles varies in the different species, and the development of different muscles can be correlated to a certain extent with variations in function.

In most fish, the horizontal muscles are more highly developed because the eye movements are chiefly in the horizontal plane. The obliques are hypertrophied in herbivora, in which the continual up-and-down movements of the head necessitate corresponding clockwise and counterclockwise rotation of the eyes. On the other hand, the medial and lateral recti are hypertrophied in carnivora, in which the predominant head movements are sidewise.

The erect position in bipeds has led to a greater development of the muscles turning the eyes downward (the inferior rectus and superior oblique) than of muscles turning the eyes upward. The superior oblique muscle has been lengthened, and its effectivity in human beings has been increased by the development of a muscle inserting at the apex of the orbit, while the shorter inferior oblique muscle continues to insert at the margin of the orbit.

The degree of development of the extrinsic muscles is closely associated with the environmental need for ocular mobility. As the eyes come to be placed forward in the head, the only way in which panoramic vision can be maintained is by greater ocular mobility. In studying ocular mobility, it should be remembered that the primitive function of

the eye muscles was not to aim the eye at objects.

The original actions were reflex and involuntary, designed to give the eyeball the attributes of a gyroscopically stabilized ship, for the purpose of maintaining a constancy of visual field despite chance buffetings and twistings of the animal's body by water currents and so on. This primitive type of eye movement is seen in the lower types of vertebrates and is in keeping with environmental needs.

The primitive function of the eye is best illustrated in the simpler types of fish. The vast majority have only reflex, involuntary eye movements. In fish whose eyes are placed laterally, every turn of the head is accompanied by a compensatory turning of the eye. A moving object is never followed by an eye movement; instead, the fish (having no neck ordinarily) bends or turns the whole body so as to face the interesting object and keep it in the binocular field. In aquarium specimens, "wheel" movements of the eyes can often be clearly observed: This movement, obviously carried out by the two obliques, suggests that this was the primitive function of these muscles.

Most birds have relatively small, poorly developed extrinsic muscles, and the eyes are practically immobile, relying upon the flexibility of the neck; even the reflex eye movements may be greatly restricted and replaced by reflex neck movements. The amphibians are known to perform no eye movements other than retraction and elevation. Many of the more sluggish lizards have fixed eyes; likewise, in snakes, there is little spontaneous mobility.

In the matter of eye movements, mammals are at once set off from all other vertebrates by the fact that whenever voluntary movements are possible at all, the two eyes are never independent but are always conjugated. The eye movements in mammals are always most extensive in the plane of greatest biologic usefulness, which is usually horizontal.

Spontaneous eye mobility is greatest in the higher primates, which alone among mammals have a fovea; but even here it is supplemented to a surprising degree by head movements. Spontaneous mobility is next best developed in the larger carnivores, particularly the cat and dog families. Voluntary eye movement seems best developed in man.

It is therefore evident in our study of the development of the extrinsic muscles in man, that environmental influences play an important role and, because of the complex environmental needs, a highly complicated binocular mechanism is present in which the extrinsic muscles are modified to cope with the visual requirements.

This fact appears to be associated with the progressively forward position of the eyes and the development of foveal vision. As the eyes come to be placed forward in the head, the only way in which panoramic vision can be maintained is by greater ocular mobility. In his binocular development, man's eyes are always conjugated and voluntary eye movement seems best developed. As a result of this development he must have not only a wide field of vision, but also foveal fixation, an essential for his field of greatest need, namely down-and-in vision.

3. The anatomic picture seen at the various stages of development of the extrinsic muscles, although conforming in a general way to the mature stage, showed certain features characteristic of the particular stage of development.

The series of specimens examined by me was selected from a larger group and represents as near as could be determined the following stages of development: 40 mm., 75 mm., 140 mm., 260 mm., 375 mm., 450 mm., 500 mm. (birth), two years of age, 11 years, and the mature eye. (The measurements represent the crown-to-heel length.)

The series was started at the 40-mm. (two and one-half month) stage for four reasons: (1) Embryonic changes previous to this have been extensively studied and the recent work of Gilbert¹,² has given us a very

complete picture of the early embryonic stage; (2) the development following this early embryonic stage has not been completely studied and certain gaps in our knowledge still exist; (3) it is believed that a study of the later development of these muscles may reveal some tangible evidence of their physiologic and anatomic nature; (4) the 40-mm. stage was the earliest stage possible to dissect satisfactorily.

The early specimens were dissected under water using magnification. Although certain phases of the muscle arrangements (such as the muscle insertion) could not be clearly determined in the early specimens they revealed certain data which seem significant.

The study of the various specimens revealed the following:

A. 40 MM. (TWO AND ONE-HALF MONTH) SPECIMEN (fig. 1)

The diameter of the eyeball was one mm.

The angle between the optic axes was about 70 degrees.

The length of the muscle cone could not be determined. The muscles, although poorly defined, could with care be recognized especially at the points of insertion. The muscle bodies were pale and had much the same appearance as the surrounding tissue with which they blended without a sharp line of demarcation. The origin third of the muscle cone could not be satisfactorily dissected as it seemed to merge with the surrounding membranes. The rectus muscles were inserted at the equator of the globe and the insertion points were fairly well defined.



Fig. 1 (Fink). Drawing of a 40-mm. (two and one-half month) human specimen.



Fig. 2 (Fink). Drawing of a 75-mm. (three month) human specimen.

These muscles were proportionally thick and short as compared with the later stages.

The obliques could be defined but like the recti blended with the surrounding tissue. Their insertions seemed to blend with the adjacent rectus insertion. Their angulation in relation to the globe appeared to be between 40 degrees to 45 degrees. The superior oblique tendon was broad in proportion to its length as compared with its later development.

B. 75 MM. (THREE MONTH) SPECIMEN (fig. 2)

The diameter of the globe was three mm.

The angle between the optic axes was about 65 degrees.

The rectus muscles were fairly well defined and although they merged with the surrounding tissue they could be readily separated. The muscle cone was about five mm. long, and the points of origin of the muscles were indefinite although much less so than in the previous specimen. The muscle bodies were proportionally thicker in comparison to their length than found in later specimens. The insertions were near the equator and could be easily determined.

The obliques were fairly well defined and like the recti merged with the surrounding tissues. Their insertions could be accurately determined and seemed to blend with the adjacent rectus. With careful dissection it was evident that the lines of insertion were posterior to the rectus insertion.

The oblique insertions seemed nearer the equator than in the adult eye. The angle of

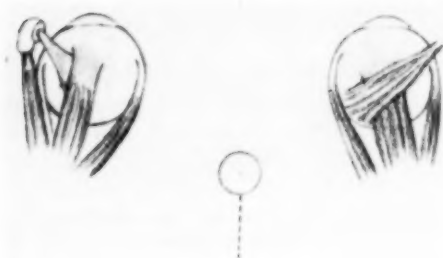


Fig. 3 (Fink). Drawing of a 140-mm. (four month) human specimen.

the oblique muscle planes with the anterior posterior vertical plane of the eye was about 45 degrees.

The reflected portion of the superior oblique was almost round and tendinous in appearance. There was an acute angle (30 degrees) between the two parts of the superior oblique.

C. 140 MM. (FOUR MONTH) SPECIMEN (fig. 3)

The diameter of the globe was six mm.

The angle between the optic axes was about 65 degrees.

The length of the muscle cone was about 10 mm. The muscles were somewhat narrower in proportion to their length than seen in the previous specimens.

The origins of the recti were well defined and their insertions encircled the equator of the globe. The muscle bodies were sharply defined and easily separated from the surrounding tissue.

The oblique muscle planes made an angle of about 45 degrees with the anterior-posterior vertical plane of the globe.

The two parts of the superior oblique formed a less acute angle (about 35 degrees). The reflected portion of the superior oblique was well defined and cordlike in appearance. The oblique insertion showed a more definite separation from the adjacent rectus and could be more easily traced to its insertion just posterior to the equator.

D. 260 MM. (FIVE AND ONE-THIRD MONTH) SPECIMEN (fig. 4)

The diameter of the globe was 10 mm.

The angle between the optic axes was about 65 degrees.

The length of the muscle cone was about 14 mm. The muscles were more clearly separated than in the previous specimens and were longer and narrower in proportion than previously seen. The points of origin were more evident. The rectus insertions were better defined and encircled the globe at about the equator.

The oblique planes made an angle of about 45 degrees with the anterior-posterior vertical plane of the globe. The superior oblique showed an angle of about 45 degrees between its two parts. Its reflected tendon was better defined and its insertion could be clearly made out more posterior to the equator but seemingly more anterior than in the mature eye.

The inferior oblique likewise showed a more defined insertion and also not so far posterior as the adult eye.

E. 375 MM. (SEVEN AND ONE-THIRD MONTH) SPECIMEN (fig. 5)

The diameter of the globe was 13 mm.

The muscle cone was about 18 mm. long.

The muscles were well defined and were longer and narrower than in the previous specimens. The origins and insertions of the recti were more evident and the insertion end of the muscles took on a more definite tendinous appearance.

The oblique muscle planes made an angle of about 45 degrees with the anterior posterior vertical plane of the globe. The superior



Fig. 4 (Fink). Drawing of a 260-mm. (five and one-third month) human specimen.



Fig. 5 (Fink). Drawing of a 375-mm. (seven and one-third month) human specimen.

oblique showed an angle of about 45 degrees between its two parts. The superior oblique tendon was round and tendinous in appearance and inserted slightly more posterior to the equator than described in the previous specimen.

The inferior oblique insertion was also more evident and more posterior to the equator than in the previous specimen.

F. 450 MM. (NINE MONTH) SPECIMEN (fig. 6)

The diameter of the eyeball was 15 mm.

The muscle cone was about 21 mm. long.

The muscles presented much the same picture as previously described except that they were somewhat better defined and more easily separated from the surrounding tissue. Also they were proportionally longer, less broad, and thinner. The origins and insertions of the recti were more defined and took on more the appearance as seen in the mature development.

The oblique planes were as described in the previous specimen and the angle between the two portions of the superior oblique was less acute (about 50 degrees). The insertions



Fig. 6 (Fink). Drawing of a 450-mm. (nine month) human specimen.



Fig. 7 (Fink). Drawing of a 550-mm. (full term) human specimen.

of the obliques were more defined and somewhat more posterior.

G. 550 MM. (FULL TERM) SPECIMEN (fig. 7)

The diameter of the eyeball was 17 mm.

Length of the muscle cone was about 25 mm.

The muscles showed most of the characteristics of the mature eye except that they were shorter, somewhat thicker, and broader. The rectus insertions were near the equator.

The oblique planes made an angle of about 45 degrees with the anterior-posterior vertical plane of the globe. The oblique insertions were slightly more posterior than previously described and seemingly the same as found in mature eyes.

H. TWO-YEAR-OLD SPECIMEN (fig. 8)

The diameter of the globe was 20 mm.

The picture was similar to that described in Figure 7, except the muscle cone was about 30-mm. long and the muscles were not so broad or thick. The line of insertion of the recti seemed somewhat more posterior to the equator than seen in previous specimens, apparently due to the proportionately

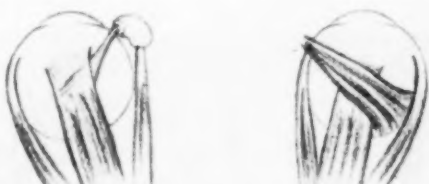


Fig. 8 (Fink). Drawing of a two-year-old human specimen.

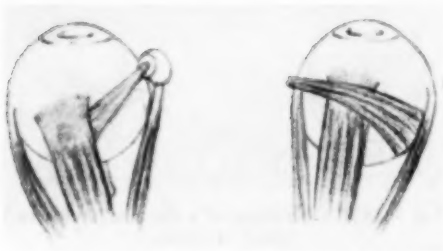


Fig. 9 (Fink). Drawing of an 11-year-old human specimen.

greater expansion of the anterior segment of the globe.

The obliques showed much the same picture as described in Figure 7.

I. 11-YEAR-OLD SPECIMEN (fig. 9)

The diameter of the globe was 22 mm.

The muscle development of the specimen was, in general, similar to the mature eye except that it was proportionally smaller. The muscles were somewhat shorter in proportion to their width than seen in the adult.

J. ADULT SPECIMEN (fig. 10)

The muscle development was proportionally larger than in the previous specimen and the muscles were somewhat longer than in proportion to their width.

B. DEVELOPMENTAL FACTORS RELATED TO THE ORIGIN AND INSERTION OF THE EXTRINSIC MUSCLES

I. DEVELOPMENT OF THE ORIGIN

As indicated previously, the point of origin of the muscles in the 40 mm. specimen could not be determined by dissection even though

magnification was used. They were not well demarcated and seemed to blend with the surrounding membranes. In the 75-mm. specimen more evidence of the point of origin could be seen but continued to be poorly defined. The point of origin became increasingly more definite in the later specimens as previously described.

In considering the point of origin of the ocular muscles in man a broader appreciation is gained by studying the origin of the lower forms.

In general, it may be said that in the lower forms in which the globe almost completely fills the orbital cavity, the rectus muscles show extensive line-shaped origins and are somewhat separated. In vertebrates with a deeper orbit, the muscles arise closer together, sometimes from a common origin. In the ascending series, as found in animals, we find a crowding together of the origins of the rectus muscles around the site of entrance of the optic nerve, and their relative positions remain essentially the same as in the lower vertebrates.

The arrangement of the origin of the oblique muscles in the various classes of lower vertebrates shows but slight variation. They arise together from the inner, anterior wall of the orbit. In birds, reptile, and fish (figs. 11 and 12), the superior oblique is the counterpart of the inferior.

In mammals, the superior oblique is greatly lengthened and its origin has moved back toward that of the recti. Its sideways approach to the eyeball was preserved throughout the backward migration of its origin by the development of a tough ring



Fig. 10 (Fink). Drawing shows the mature human eye. The muscle development was proportionally larger than in the specimen in Figure 9 and the muscles were somewhat longer in proportion to their width.

or pulley, through which it passes. The pulley is formed at the old submammalian site of attachment of the muscle on the anterior nasal orbital wall and serves to retain the original direction of action of the muscle.

A better understanding of the unusual arrangement of the origins of the oblique muscles is obtained by studying their early embryology.

Gilbert² describes the early embryonic development of the oblique muscles as follows: The study of a 12-mm. cat embryo shows that the medial end of the superior oblique anlage lies close to its point of origin on the developing orbital wall.

The distal end of the superior oblique anlage has begun to turn and extends to a point on the eyeball slightly dorsal and caudal to the anterior peripheral condensation. The bend in the superior oblique anlage marks the point about which the trochlea will soon develop. It is significant that the distal end of the superior oblique condensation has changed its direction before the anlage of the trochlea appears.

In the 50-mm. embryo the developing superior oblique can be traced to its insertion on the globe adjacent and medial to the insertion of the superior rectus. The trochlea is first observable in embryos of 15 mm. as a condensation investing the bend in the superior oblique anlage.

The inferior oblique likewise shows un-



Fig. 12 (Fink). Drawing showing the relation of the insertions of the obliques to the adjacent rectus in the chicken. The insertions of the obliques are well forward and blend with the insertion of the adjacent rectus. This arrangement produces wheel-movements of the eyeball.

usual early embryonic changes. As described by Gilbert, it was originally connected with the distal portion of the anlage of the inferior rectus. The connection between the inferior rectus and inferior oblique anlagen becomes in older embryos increasingly more tenuous, the two being connected in embryos of 12 mm. by a slender cord of cells. By 12.5-mm. stage, the two anlagen are entirely separated and from the point of junction with the inferior rectus, the inferior oblique grows in two directions—cranioventrally and caudo-dorsally. By 26 mm., the cranioventrally directed extremity has reached its point of attachment to the orbital surface of the maxilla, and the caudodorsal extremity has inserted on the sclera adjacent and medial to the insertion of the lateral rectus.

2. DEVELOPMENT OF THE INSERTION

The insertion of the rectus muscles as found in the series of specimens examined has been considered in the previous section. In general in the early stages the position of the insertions was very near the equator of the globe. However, in the 500-mm. specimen, there was a tendency for the segment of the globe anterior to the insertion of the muscles to become proportionally larger than the posterior segment and cause the line of insertion of the muscles to be slightly posterior to the equator.

This tendency was most evident in the two-year-old specimen but in the 11-year specimen the various points of insertion returned to a position near the equator of



Fig. 11 (Fink). Drawing showing the relation of the insertions of the obliques to the adjacent rectus in the fish. The obliques originate close together, far forward, and share insertion sites with the adjacent rectus. This arrangement indicates that the function of the obliques is to impart compensatory reflex wheel-movements to the eyeball in the plane of its equator.



Fig. 13 (Fink). Drawing showing the relation of the insertions of the obliques to the adjacent rectus in the rabbit. The oblique insertions are far forward and blend with the adjacent rectus.

the globe due to the growth of the posterior segment of the globe.

The arrangements of the oblique insertions as found in the various specimens have been described in a previous section. They conform to a definite pattern throughout the series. In the first three specimens the superior oblique insertion seemed to blend with the superior rectus insertion, and seemed more anterior than was observed in the later specimens. This may have been more apparent than real because of the poorly defined state of the tissues.

In the 140-mm. specimen, the insertion was more definitely defined and could be seen

posterior to the rectus insertion. This posterior position was increasingly evident in the later specimens and in the 500-mm. specimen the superior oblique insertion seemed to have almost reached the position on the globe as found in the more mature specimens.

The position of the insertion of the inferior oblique seemed more defined even in the early specimens. The position of the insertion in the two early specimens seemed to blend with the adjacent rectus and the insertion was indefinite. In later specimens the insertion was posterior to the rectus insertion and changed but little in its position during the later developmental process except for a progressive backward shift. The two-year and the 11-year specimens showed the inferior oblique insertion in practically the same relationship as seen in the mature specimen.

The most impressive evidence of the influence of environment on the development of the extrinsic muscles is found in a comparison of the insertion of the oblique muscles as found in the various species.

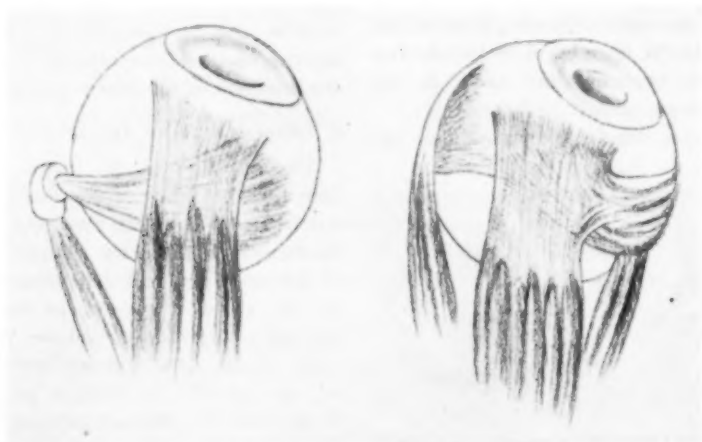


Fig. 14 (Fink). Drawing showing the relation of the insertions of the obliques to the adjacent rectus in the ox. The oblique muscles originate more posterior than in the rabbit, and are inserted nearer the equator of the globe. The oblique muscles are hypertrophied in herbivora, because the continual up-and-down movements of the head necessitate corresponding clockwise and counterclockwise rotation of the eyes.



Fig. 15 (Fink). Drawing showing the relation of the obliques to the adjacent rectus in the dog. The oblique muscles originate more anterior than in the ox. The horizontal muscles are hypertrophied in carnivora in which the predominant movements are sidewise. The obliques show less vertical function and greater rotation action.

In the lower vertebrates, where the obliques originate close together, they share insertion sites with the adjacent rectus muscle and the insertion is anterior to the equator. This arrangement indicates that the original function of the obliques was to impart compensatory reflex wheel movements to the eyeball in the plane of its equator.

In the fish and chicken (figs. 11 and 12) the insertion of the obliques is well forward. In higher vertebrates in which the origin of the superior oblique has the same general arrangement as in man, the oblique muscles are also inserted near the tendon of the superior and lateral rectus muscles.

In the rabbit the insertions (fig. 13) are farthest forward of the mammals examined. In the ox, dog, and pig (figs. 14, 15, and 16), the oblique muscles are inserted slightly more posteriorly on the globe. In the monkey (fig. 17), the oblique muscles are inserted posterior to the equator and closely resemble the position as found in the human oblique muscles.

The relation of the insertion of the obliques to the superior and inferior recti is of interest. In the various species the two obliques cross the recti, sometimes between them and the globe, sometimes outside them. In man, the superior oblique passes inside, the inferior outside, the corresponding rectus. In fish both obliques are outside. In birds, in elephants and chimpanzee, the inferior oblique is outside; but in other mammals it is usually inside. In the tiger, the obliques split to enclose the rectus; in the lion and the tortoise, the superior rectus pierces the superior oblique, and the inferior oblique pierces the inferior rectus.

C. DEVELOPMENTAL FACTORS RELATED TO THE POSITION OF THE EYE

According to Mann³ up to the seven-mm. stage, there is no angle between the optic axes in man, both optic stalks lying in the same straight line. As the maxillary process increases in size, its mesoderm begins to extend not only forward but also upward be-

Fig. 16 (Fink). Drawing showing the relation of the insertions of the obliques to the adjacent rectus in the pig. In the pig the oblique muscles are placed anterior to the equator and are much the same as in the dog.





Fig. 17 (Fink). Drawing showing the relation of the insertions of the obliques to the adjacent rectus in the monkey. The oblique muscles are inserted in the posterior lateral quadrant of the globe and make an angle with the anterior-posterior plane of the globe of about 45 degrees. The function is predominantly elevation and depression with rotation and abduction present to a moderate degree.

hind the eye. This is associated with an increase in width of the skull base in this region, and, with a secondary movement of the eye forward and inward, the angle between the optic axes becomes apparent.

This angle then steadily decreases from 160 degrees at nine mm. to 72 degrees at 40 mm. After this stage, the process is continued for a short time at a rapidly decreasing rate; the final angle between the optic axes is usually in the neighborhood of 60 degrees.

The orbital development is closely related with the development of the optic axes. The forward extension of the maxillary process is associated with a swinging forward of the axes of the orbits, and follows the visual axes of the eyes quite closely. Stabilization of the orbital position is reached at about 45 degrees.

It is interesting in this connection to study the changes in position of the eyes of the lower forms. In vertebrates lower in the scale than mammals, the eyes are laterally placed and the fields of vision do not overlap. In some, however, a change takes place in the optic axes as in the case of certain of the birds (notably owls) in which the eyes look more forward and there is the possibility of a certain amount of binocular vision.

Among the mammals the position of the eyes varies. The noncarnivora such as the rabbit, ox, and sheep have the eyes laterally placed. The first definite displacement of the

eyes from their primitive position at the sides of the head appears in the carnivora, in which the eyes look straight forward and the fields of vision overlap. This is seen in such animals as the dog, cat, and monkey.

The development of the maxillary process and the swinging round of the eyes in the higher mammals may both be regarded as correlated with the increasing size and complexity of the central nervous system. We have, therefore, with this widening of the brain in mammals, a decreasing angle between the optic axes thus making possible binocular vision.

As in the lower forms, the position of the eyes in man influences the development of the extrinsic muscles. In the process of development, the eyes of man and monkey change their position more than any other form. However, in the examination of this group of human specimens the relation of the muscle planes to the anterior-posterior plane of the globe showed a surprisingly small variation and, generally speaking, retained a fairly constant relationship. This was true even in the very early specimens where the position of the eyes showed the greatest degree of change in relation to the surrounding structures.

As was the case of the recti, the obliques showed comparatively little variation of the line of action of the oblique planes in their relation to the anterior-posterior plane of the globe. In the various specimens examined the oblique muscle planes seemed to vary but little in their relation to each other and formed an angle of about 45 degrees with the anterior-posterior vertical plane of the eye. However, in the 40-mm. specimen, the angle of the oblique planes was difficult to determine because of the immature state of the tissues.

The angle formed by the proximal and distal portions of the superior oblique at the trochlea (trochlear angle) is of interest. According to Gilbert² in embryos of 17 mm. the angle is obtuse, but subsequently becomes less and less so until, in embryos of 50 mm.,

the trochlear angle appears to be acute. This increase in the acuteness of the trochlear angle during later development may be the result of the forward shifting of that portion of the frontal bone to which the trochlea is attached.

In the 75-mm. and 140-mm. specimens examined by me, the trochlear angle was about 35 degrees. The 260-mm. specimen showed an increase in the angle to be about 40 degrees. The angle gradually increased and at birth (550 mm.) the angle was about 55 degrees which is practically the same as in the mature eye.

The variation in the trochlear angle in animals is of interest. Poole⁴ measured the angle between the two parts of the superior oblique before and after passing through the trochlea. His findings are as follows:

ANGLE BETWEEN TWO PARTS OF SUPERIOR OBLIQUE		(degrees)
Bullock	100	
Sheep	99.5	
Rabbit	54	
Pig	91	
Cat	79	
Monkey	36	

COMMENTS

From the series of specimens considered in the preceding pages, certain data are obtained concerning the development of the extrinsic muscles of man which may be of value in furthering our knowledge relating to the anatomy and physiology of these muscles.

These factors seem evident:

1. Even at the earliest stages of development the arrangement of the extrinsic muscles in relation to the eyeball is, generally speaking, much the same as in the adult.

2. A comparison of the planes of action of the extrinsic muscles in the various periods of development shows a fairly uniform relationship between the planes of the muscles and the anteroposterior vertical plane of the eyeball. This constant relationship between the globe and the muscle planes was espe-

cially evident in the arrangement of the oblique muscles and was seen in even the earliest specimens. The planes of the superior and inferior oblique muscles were quite similar to each other and formed an angle of about 45 degrees with the anterior-posterior vertical plane of the globe.

It is possible that this anatomic factor, in conjunction with the innervational influence, tends to create a stability of the vertical mechanism. Such stability of the vertical mechanism permits a flexibility of its horizontal component and makes possible the complex integrated action of the vertical mechanism.

3. The angle formed by the muscular portion of the superior oblique and its tendon varied. This variable angle is apparently due to the variable position of the eyeball in its relation to the growth of the brain.

4. The influence of environment is especially evident in the oblique muscle development.

In the lower vertebrates, the insertions of the obliques were in all cases more anterior to the equator of the globe, and in certain species were so far forward that they blended with the insertion of the adjacent rectus muscles. This forward position of the insertion indicates that their function is rotation and adduction and this action is in proportion to the amount the insertion of the oblique is anterior to the equator of the globe.

In man and monkey the insertion of the obliques are in the posterior lateral quadrant of the globe. The obliques act predominantly to elevate or depress the eye, and to a less degree to abduct and rotate it when in eyes front position.

5. This study emphasizes that the superior oblique in man is a highly specialized muscle adapted to our mode of life, whereas the inferior oblique muscle resembles closely the muscle of the lower vertebrates and performs a minor role in man as compared to the superior oblique. In addition to counterbalancing the mechanical action of the powerful inferior oblique, the superior

oblique has the capacity for highly specialized functions made possible by the long intricately developed tendon. Because of his erect position and the need for a wide latitude in the flexible field of foveal vision in which downward gaze predominates, man has acquired a muscle which permits such activities.

CONCLUSION

This presentation is based upon a study of a series of human specimens in which the successive stages of development of the extrinsic muscles are noted. The specimens studied cover the period from the 40 mm. stage to maturity.

Gilbert's¹ monumental work, which has just been completed, has added appreciably to our knowledge of the very early embryonic extrinsic muscle changes in man. The present study begins where Gilbert's study (early embryologic period) stopped, and carries the development to maturity;

thus completing the entire period of development of the extrinsic muscles in man.

Because of the state of uncertainty which exists concerning the later development of the extrinsic muscles, various pertinent facts are assembled concerning this phase of their development, some of which are known and some of which have been determined in this study.

Such a presentation is not all inclusive but rather a step toward the completed picture, and many wide gaps in our knowledge concerning extrinsic muscle development will remain. It is hoped, however, that this study will assist in clarifying some of the more obscure phases of extrinsic muscle development and bridge over certain gaps in our knowledge of the anatomy and physiology of the extrinsic muscle which may provide answers to some of the controversial clinical problems.

Medical Arts Building (2).

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DISCUSSION

DR. LEON S. STONE (New Haven, Connecticut): I am very much interested in this subject and its relation to the well-known fact that the embryonic eye induces the muscles to form. For example, one can control the size and position of the muscles by exchanging eyes between two amphibian embryos, one of which has a very small eye and the other a very large one. By placing a large eye in a small animal the developing ocular muscles become almost twice as large as those on the control side.

Furthermore, if one compares the eyes exchanged between the small and the large hosts, there is a very definite demonstration that not only does the large embryonic eye induce the mesenchyme of the smaller animal to produce very large muscles, but in the reverse experiment the smaller eye on the larger animal will be accompanied by smaller muscles than on the opposite control side of that host.

I have always felt that there were many opportunities to examine further the influence of the eye on the development of the ocular muscles and their positions by this kind of experiment. A good analy-

sis could be made in this field which is not yet widely explored.

DR. WALTER H. FINK: In my completed paper I have stressed environmental influence, since it plays a very important role. As Dr. Stone has pointed out and as I have also indicated in my paper, this environmental factor is very important in determining individual development. For example, certain species, such as the bird with its large eyes, has a poorly developed ocular musculature which is a counterpart of that of man. This has resulted from the fact that the bird does not rotate his eyes but scrutinizes the field of vision by moving his neck instead.

The influence of environment on man is very pronounced and follows a very definite pattern of development determined for his environmental conditions.

DR. LORAND V. JOHNSON (Cleveland, Ohio): Dr. Fink is to be congratulated on this fine paper.

One thing I want to point out is that anyone who has looked carefully at the insertion of the superior oblique when it seemed to be parietic (at the time of a shortening or advancement operation) has noticed that there are times when the superior oblique comes up, remains attached and adherent to the superior rectus at this point, and then runs backward to its insertion. That is the thing that has always seemed curious to me—why this muscle could come so far forward to be adherent. In an article I published on this subject two years ago, I called that finding "with the superior oblique carried forward." Obviously I must make a correction—it has not been carried forward; it has simply grown to this position, stayed there, and continued back.

The defect, of course, is obvious: Instead of the superior oblique acting as the depressor, its insertion is up at the insertion of the superior rectus and, as a result, it cannot depress the eye. If anything, it would act to elevate the eye further.

I am sure all of you who have separated those adhesions at that point, and have allowed the superior oblique to fall back so that its insertion can be normal, have found that those patients have had normal depression without any shortening procedure on the muscle.

DR. FINK: Dr. Johnson made a very significant contribution to our knowledge of superior oblique anatomy when he published his work on abnormal development of the fascial sheath of the superior oblique muscle. Although our present knowledge of abnormal fascial superior oblique sheath development is incomplete, it is evident that such conditions are present in a certain number of cases. Such data are difficult to obtain because postmortem changes alter the picture appreciably.

In a series of cases discussed in my paper, the

fascial fusion between the superior oblique tendon was very definite and, in the earlier specimens, it appeared that the two were intimately fused. A study of the later stages shows lessening of this fusion and more flexibility of union.

It seems to me that abnormal sheath development could very easily occur with a deviation in the normal process resulting in abnormal adhesions between the tendons of the two extrinsic muscles.

DR. HERMANN M. BURIAN (Iowa City, Iowa): Dr. Fink's thesis is that there is a very stable development of the oblique muscles which, in his opinion, speaks for a physiologic stability or stability of action. This he believes to be desirable and he also thinks that the horizontally acting muscles require greater pliability for proper functioning.

I wonder whether Dr. Fink could tell us why he considers the obliques to be more stable in their development than the horizontal muscles. Isn't it possible that the greater stability of the vertical mechanism as compared with the horizontal mechanism—if such a difference really exists—is due to the differences in the innervation of the various muscles in the normal use of the eye?

DR. FINK: My presentation today is an effort to add to our fund of knowledge concerning the stability of the vertical muscles and the data presented in my paper demonstrate a very definite pattern of development from the early onset of embryonic life. This seems to suggest that nature has provided for the complex action of the vertical muscles by establishing from the earliest onset a very stable pattern. One can possibly conclude that any disruption of this stable pattern would explain the marked disturbance which results in a paresis of one of the vertical muscles.

CHANNELS IN THE HUMAN LENS CAPSULE AND THEIR RELATIONSHIP TO SENILE CATARACT

ROBERT HUGH MONAHAN, M.D.*
Saint Paul, Minnesota

INTRODUCTION

Since the late 19th century, both ophthalmologists and anatomists have sought to explain the behavior of the lens capsule. Described as a homogeneous structureless membrane, its permeability is that of a finely regulated sieve, permitting the passage of substances of small molecular size and blocking those whose particle size approaches the visible range.

The present study will demonstrate that this hitherto unexplained permeability exists because of a complex system of channels which course through the periphery of the lens capsule, permitting the entrance of modified aqueous into the lens.

Until one is aware of the nature of these channels, one tends to doubt that a structure as complex as this could have been in existence for these many centuries without previously having been described. However, a complete description would have been impossible without the development of the phase-contrast microscope.

The channels are so small and their index of refraction so similar to that of the surrounding lens capsule that their detection is close to impossible with the ordinary light microscope. Rarely, a routine slide of the lens demonstrates the defects at the periphery sufficiently to suggest that internal structure is present in the lens capsule but, even then, the relatively gross optical sections made by the ordinary light microscope make it diffi-

cult to locate the level of the structure being examined within the capsule.

Time prevents describing completely the phase-contrast method. Since its discovery by Zernike in 1934, it has been developed so rapidly that, since World War II, it has become an accepted method of tissue examination.

Several differences exist between the phase-contrast microscope and the ordinary light microscope (to which we are more accustomed); and it is these differences which make it possible to see the lens capsule channels.

The main advantage of the phase-contrast microscope is its ability to convert phase differences into intensity differences, thus making apparent structures which usually are transparent. Other advantages of the phase-contrast instrument are its more accurate definition at the critical focus, the thinner optical sections, and its increasing accuracy as dissimilar points approach each other in similarity. Each of these differences offers advantage in the study of transparent structures; and considered together they make the instrument an ideal tool for the study of the lens capsule.

DESCRIPTION LENS CAPSULE

The lens capsule usually is described as a thin, transparent, homogeneous, structureless, firm elastic membrane. Despite the fact that this is the standard description in the literature, there have been suggestions that it is not structureless and not homogeneous. Becker, Schirmer, and Berger all did digestion experiments on the lens capsule in the 19th century. They noted that nitric acid or potassium permanganate caused the capsule to swell and dissolve but, before dissolving, it broke up into zigzag steps.

* Formerly a fellow in pathology, Massachusetts Eye and Ear Infirmary, and teaching fellow in ophthalmology, the Harvard Medical School.

I wish to express my sincere thanks to Dr. Parker Heath, director of the Eye Pathology Laboratory, Massachusetts Eye and Ear Infirmary, under whose direction this problem was studied, for his counsel and encouragement. The instruments were provided by the Kresge Eye Pathology Fund.

These steps suggested that the equator is not homogeneous and led to the description of the capsule as a laminated structure, but the reason for the steps in the capsule proper never has been explained. It now appears that the lens-capsule channels cause areas and planes of relative weakness in the capsule which give away during digestion and teasing to produce the laminated appearance.

Another unusual reaction during digestion is the tendency for the capsule to dissolve first on the inner side and from there outward. This in itself almost could be considered proof that defects are present, but the failure to demonstrate the defects has caused this information to be shelved with other interesting but unexplained phenomena. The fact that the lens capsule channels give free access to the inner surface now explains why acid can pass through the capsule to dissolve it from the inner surface before it dissolves the more resistant outer surface.

For a long time the permeability characteristics of the lens capsule have been known to be consistent with a membrane in which there are relatively gross defects. It is freely permeable to water, electrolytes, alcohol, and a large number of substances such as dyes of fairly large molecular size. However, in the range of very large particles, those whose size is just below the limits of resolution of the microscope, there is a sudden drop in permeability.

Substances to which the capsule has limited permeability are vital red, hemoglobin, egg albumen, stilbene blue, and eric violet. The last two have a positive charge which tends to delay their passage through the negatively charged capsule. The still larger particles of Congo red, colloidal iron, night blue, and India ink are unable to pass through the membrane. This filtering effect led Friedenwald to search for pores in the capsule, which he finally concluded must be submicroscopic.

Dr. Parker Heath has a large number of sections from an eye into which India ink was injected prior to enucleation. These

slides present a jet-black anterior chamber, posterior chamber, and zonular region. By contrast the lens remains perfectly clear. Even though the phase microscope shows that there are patent channels in the capsule, the size of the particles is too large to gain access to the lens tissue.

METHOD OF EXAMINATION

The method of examination proved to be rather time consuming. The channels first were observed in the equatorial zone of the capsule. Before they were seen, the area had been examined with the $\times 10$, $\times 20$, and $\times 43$ (NA 0.25, 0.50, and 0.66, respectively) objectives with ordinary light microscopy, and with dark contrast-medium phase at all powers.

When the microscope was changed to the $\times 97$ oil immersion (NA 1.25), the lens capsule still appeared structureless and homogeneous. However, with the introduction of the annular diaphragm, permitting the use of the dark medium-phase contrast objective, the lens capsule was seen to be filled with minute linear streaks. Subsequent examination showed that linear streaks may also be seen easily with the bright high contrast, bright low contrast, and B-minus low contrast, oil immersion objectives. For routine examination the dark M proved of greatest value.

Several thousand sections, representing several hundred specimens, were examined before the exact details of the capsule were worked out. At the same time, operative specimens were examined to determine the presence of channels in fresh lenses. Following this, a series of normal human eyes obtained from the Boston Eye Bank was examined and compared with various animal eyes. Finally, animal work was done on the experimental production of cataract in the light of the knowledge gained.

ANATOMIC ENTITIES

After the optical defects in the capsule were found, the first problem was to prove

their existence as anatomic entities. For the purpose of the experiment, it was first assumed that they were artefacts. However, each attempt to reproduce them by artefactual means failed. The following are some of the indications that the lens capsule channels are anatomic entities and not artefacts:

1. They have a definite and constant location in the lens capsule.

2. They are present in the same direction relative to the lens axis despite any change in the direction of the microtome cut. Specimens examined from eyes cut horizontally, sagittally, coronally, and at various oblique angles all demonstrate their constant position.

3. Lenses mounted in nitrocellulose or in celloidin show the channels well. They have been seen in paraffin sections but the distortion from shrinkage makes this an unsatisfactory method for examination.

4. Teased specimens show that the defects are not stress lines, a possibility that was considered early in the examination.

5. Their occasional appearance with ordinary light microscopy proves them not to be a defect introduced by the phase-contrast method.

6. They have the appearance of channels.

7. They can be filled with stains.

8. They possess branches.

9. Selective examination with the various phase-contrast objectives show them to be of lower optical density than the surrounding lens capsule.

10. Various areas in the capsule maintain a constant relationship to each other, even when the capsule is broken and very tortuous.

11. They explain the selective permeability of the lens capsule and some of its actions in pathologic conditions.

SIZE OF CHANNELS

The next aspect of the problem to be considered is the size of the channels. The larg-

est visible channels are about 0.5 microns in diameter. The smallest visible channels are at the limit of resolution of the microscope or slightly under 0.2 microns. However, some of the physiologic actions of the capsule suggest that there are channels below the visible range.

The term "channel" rather than "pore" is used advisedly. Webster states that a channel is "a closed course or conduit through which anything flows." This seems much more accurate in describing these structures than the word "pore" which is a minute opening. If the term "pore" is to be used at all in this description, it probably should be reserved to describe one of the openings of the channels where they communicate with the posterior aqueous chamber.

In contrast to the usual description given of the lens capsule, the following differences are believed to exist. It is not laminated, and it is not structureless. The capsule contains channels, and it is the location of the different types of channels that divides the lens capsule into its various zones.

In the following description of the zones of the lens capsule with its channels one must keep in mind that we are dealing with a three dimensional object, a hollow spheroid. The point where the axis of the lens joins the anterior surface—that is, the anterior pole—is used as the starting point of the description.

Surrounding this point on the anterior surface for a distance of approximately three mm. in all directions, the lens capsule is clear and devoid of channels. This is the *alpha zone*. At this distance (three mm.) from the anterior pole, there appear channels of very fine dimension (just within the limits of resolution of the phase microscope).

The channels enter the capsule at an angle of 15 to 20 degrees and course toward the equator of the capsule in a direction that would appear radial to the anterior pole when viewed from the front. This area, in which the channels enter the surface and are

parallel to each other but oblique to the surface and in which they do not occupy the entire thickness of the capsule, is designated as the *beta zone*.

As the channels course still farther toward the equator they come to occupy the entire thickness of the capsule. They are still fine in dimension and remain parallel to each other. This is the *gamma zone*.

Progressing still more equatorially the channels enter the *delta zone*. Here they are in their most interesting state. The channels become curled, twisted, branched, and tortuous. Other channels possess Y-shaped branches and extend back toward the equator. Some of them became perpendicular to the inner surface of the capsule and open into the potential spaces between the epithelial cells.

At the equator, in the *epsilon zone*, the channels are again parallel to each other and to the surface. In this region they are not branched and appear to be simple tubules in the capsule. In this zone the channels are at their largest diameter. In fact, here they are so large that their shadows sometimes may be seen with ordinary light microscopy.

Undoubtedly it was this system of parallel shadows in the equatorial portion of the capsule that led the early ophthalmic anatomists to believe that the capsule is laminated. Because they are larger here, it is in the *epsilon zone* that the channels are most easily seen even though they are usually much less numerous than in the *beta*, *gamma*, or *delta zones*.

Even in the *epsilon zone* there is no visible structure to the walls of the channels. As one examines the *epsilon zone* more posteriorly the channels become less numerous. They stop at the point where the capsule is no longer adjacent to the cuboidal epithelium although rarely an odd channel can be seen extending slightly beyond this point.

Consequently, the end of the epithelium marks the limit between the *epsilon* and *zeta* zones. As seen with the current phase-con-

trast instrument, the *zeta zone* like the *alpha zone* is clear, homogeneous, structureless, and contains no visible channels. The *zeta zone* is by far the largest since it occupies the entire posterior pole and extends almost to the equator. It differs from the *alpha zone* in that it is thinner and is not adjacent to cuboidal epithelium.

The size of the zones is somewhat variable. The discuslike *alpha zone* is the most constant in size and measures about three mm. in radius or about six mm. in diameter. The *zeta zone* is also disc-shaped and occupies almost all of the posterior aspect of the lens, consequently its diameter is approximately nine mm. The other zones are not discs but instead ribbons extending around the spheroidal lens near its equator.

Because the zonular fibers attach in the region of the *gamma* and *delta zones* anteriorly and to the *zeta zone* posteriorly, the lens capsule is raised in irregular dentations which make exact measurement impossible. However, it should be noted that the combined width of the *beta*, *gamma*, *delta*, and *epsilon zones* (the ribbon zones) is about 1.5 mm.

AGE DISTRIBUTION OF CHANNELS

One variation seen in the capsule is that encountered with variation of the patient's age. The equatorial channels are not seen in the fetus, newborn, or child. The youngest patient in our series whose specimen contains visible equatorial channels is that of a 13-year-old boy. However, a few newborn eyes showed minute defects in the *alpha zone* where there are no channels in the adult. During young adult life the channels appear to be present unless there is a pathologic condition of the lens. As a rule after the age of 60 years, the channels become less numerous.

Because specimens of children's eyes are less common than those of older patients, it is suggested that further studies be made

before final conclusions are drawn as to the exact age distribution of visible channels.

PREPARATION OF SPECIMENS

The type of fixation of the specimen does not appear to affect the channels. Eyes have been examined that were fixed in formalin, Kolmer's, and Bouin's solutions. No difference in the channels was noted.

The type of mount, however, is important. Specimens mounted in celloidin and nitro-cellulose show the channels clearly. In paraffin, the capsule channels are difficult to demonstrate. However, when one considers the amount of distortion that occurs in paraffin technique it is understandable that minute channels close to the limits of resolution of the microscope can be destroyed by this method. Another possibility is that the semiopaque paraffin interferes with the transmission of light enough to require a different phase system.

No matter what the cause, lens capsule channels have been found in paraffin sections only in exceptionally well-prepared specimens, and then with difficulty.

The dyes used are not of any great significance in demonstrating channels. The lens capsule channels are seen easily in unstained specimens. They are seen as easily with the routine hematoxylin and eosin and with Dr. Verhoeff's elastic stain. Because stained specimens are more abundant and because the focusing on a specific area is facilitated by the use of stained sections, most of the slides examined were those prepared with hematoxylin-eosin stains.

PATHOLOGIC CONDITIONS

One variation that has a marked effect on the finding of channels in the lens capsule is a pathologic process in the lens itself. The first few fresh specimens examined were obtained from the operating room following intracapsular cataract extraction and none of them demonstrated channels.

It soon became apparent that there is a close direct correlation between the presence

of channels and the state of the lens tissue. In a lens with mature cataract, they are absent; in a lens with immature cataract, they are diminished. This correlation is so close that, in some lenses, one can find a diminished number of channels associated with cortical changes on one side of a specimen although the opposite side presents well-defined channels and a normal cortex.

ANIMAL EYES

Animal eyes present still another problem. To date, the eyes of cats, dogs, sheep, cows, rabbits, guinea pigs, monkeys, and rats have been examined without finding visible channels. However, experimental work points to their presence in animals even though they cannot be seen.

The differences in permeability between the various species are not great enough to account for a channel system in the adult man and a closed membrane system in children and in animals. This suggests that submicroscopic channels also exist. In fact we have produced cataracts in animals by obstructing the channels even though they cannot be seen.

Following the method of Friedenwald, the animals were subjected to a series of eosin and gentian violet injections into the vitreous cavity. Either dye injected alone on three successive days diffuses through the vitreous, the lens, and the aqueous. The media are discolored temporarily but no serious injury is done. However, when either dye is injected for two days and on the third day the other is given, a cataract results.

Undoubtedly this occurs because of the heavy precipitate of large micellae which a mixture of these dyes produces. If the dyes are mixed and injected together, the particles are too large to enter the lens but, when given alternately, it appears that the precipitate forms within the submicroscopic channels.

CONCLUSIONS

Considering the nature of the channels, their absence in lenses with mature cataract,

their diminished number in lenses with developing cataract, and the experimental work in the production of cataract, it appears obvious that we have at hand the explanation of the cause of cataract in its most important form—the senile cataract.

The gradual loss of the channels with age and the constant relationship between absence of channels and presence of cataract appears to demonstrate that the cause of senile cataract is the loss of metabolic ex-

change in the lens brought about by the closure of the lens-capsule channels.

Several other forms of lens change—that is, complicated cataract, sunflower cataract, siderosis, radiant energy cataract, exfoliation of the lens capsule with glaucoma capsulare, and the Vossius-ring phenomenon—all appear to be related to the lens-capsule channels and will be discussed in another paper.

1034 Lowery Medical Arts Building (2).

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DISCUSSION

DR. DAVID G. COGAN (Boston): There is no doubt that Dr. Monahan's slides and pictures showed something in the human lens that may well be concerned with metabolic function.

I know Dr. Monahan will be the first to admit, however, that there is only inferential evidence that he is able to block the channels with his dyes. I am sure Dr. Monahan would welcome any suggestions as to how he might further prove or disprove his thesis.

DR. ZACHARIAS DISCHE (New York): I wonder whether Dr. Monahan considered the possibility that in the senile cataract he has also submicroscopic channels. I have certain difficulty understanding why in children and in animals these channels, in spite of their very submicroscopic size, would not interfere with the proper exchange of the nutrients, and only in the adult man this should be the case. I have difficulty understanding that.

DR. MONAHAN: I believe very firmly that there are submicroscopic channels. I think a channel system undoubtedly exists in animals and also in children, but unfortunately I can't demonstrate them. I can demonstrate them very easily in the adult human, and I think the evidence is all in favor of there being submicroscopic channels.

As Dr. Cogan pointed out, we can't prove that until we see them—and we can't see them. They are definitely submicroscopic if they are there. In the adult human we can see them very easily.

DR. DISCHE: But obviously, in spite of the submicroscopic size in animals and children, they can achieve their proper function, namely, to provide the lens with material which goes through it.

DR. MONAHAN: Oh yes, very much so.

DR. DISCHE: During the development of cataract in man that is not possible. You assume, therefore, that there is complete obstruction of the channels in the senile cataract, because they are sufficiently large in animals, despite their submicroscopic diameter, to provide an access of the nutrients to the lens. In senile cataract that is not the case any more.

Do you assume that there is a disturbance of the passage of certain essential substances to the lens, due to the destruction of the channels? Is this your thought?

DR. MONAHAN: Yes. I believe it is due to a decrease in metabolic exchange because of an obstruction of the channels. One must remember that these channels are very close to the limits of resolution. They are probably finer than most structures which we are accustomed to see. They are just at the limits of resolution of the phase-contrast microscope, which is a little finer than the limits of resolution of the ordinary microscope.

DR. COGAN: I think Dr. Dische has in mind the obliteration of the channels. Does it precede or is it a result of the cataract formation? I think either assumption is certainly valid.

DR. MONAHAN: It is a matter of cause and effect. It can't be answered, although I think the evidence points to the fact that probably the cataract results from obstruction of the channel.

DR. COGAN: The fact that you block them and get a cataract? We don't know, of course, that just the injection itself is not a sufficiently traumatizing agent to produce cataracts.

DR. MONAHAN: The injection of either dye alone, of course, will not produce cataract. It is only in the particular combination in which the dyes are precipitated that one gets a cataract.

DR. CONRAD BERENS (New York): Have you

used that for demonstrating cataract? It might be a lead. You might try it.

DR. LUDWIG VON SALLMANN (New York): May I ask Dr. Monahan whether he plans to continue his studies with the electron microscope? So far as I know, no channels have been identified with this method of examination.

DR. MONAHAN: Thank you, Dr. von Sallmann. If there had been more time I would have gone into that aspect.

Yes, the capsule has been examined quite extensively with the electron microscope. It also has been examined with the phase microscope. The particular areas in which these channels occur apparently were missed because they were not described, and all the photographs published apparently were taken at the anterior and posterior capsule rather than at the equator.

DR. M. A. LAST (New York): Did you have any cases of desquamation of the anterior capsule?

DR. MONAHAN: Yes.

(Not identified): Are there many instances in which desquamation of the lens capsule or exfoliation of the lens capsule occurred without any cataract formation?

DR. MONAHAN: Oh, yes. That brings up another complete subject for discussion. Exfoliation of the lens capsule occurs definitely in zones on the anterior surface, as you know. It occurs in approximately five zones. Those zones correspond quite well to the location of the capsule or channels in their various forms, with this exception: The zonular fibers also enters that area, which causes an additional zone to be formed. Certainly exfoliation occurs without cataract formation. We have examined slides with exfoliation, and the channels still remained patent.

DR. V. EVERETT KINSEY (Detroit): If these channels proceed just from the posterior pole toward the equator, why does Dr. Monahan feel they are so important metabolically, in view of the fact that most of the nutrition comes from the anterior portion?

DR. MONAHAN: The channels open on the anterior surface of the lens capsule.

DR. KINSEY: And proceed posteriorly?

DR. MONAHAN: And proceed equatorially. There are no channels seen in the posterior capsule.

DR. KINSEY: I am sorry; I misunderstood you.

DR. MONAHAN: They open three mm. from the anterior pole.

AN EXPERIMENTAL ANALYSIS OF LENS REGENERATION*

L. S. STONE, M.D.

New Haven, Connecticut

Throughout all of the vertebrates the lens arises in the embryo from the surface ectoderm at the point where it makes contact with the early optic vesicle. Furthermore where an embryonic eye is fully adapted to experimental tests, as in the case of amphibians (Spemann, 1938), it has been shown that this contact has particular significance; for the surface ectoderm is responding to some special influence, perhaps of a chemical nature, initiated by the developing eye.

If contact fails to take place no lens develops. If the normal presumptive lens-forming ectoderm is replaced by ectoderm taken from remote regions of the body of the same or even another species of embryo, it will also be induced by the underlying eye to form a lens instead of the skin it would have formed had it been left in its original position on the donor.

The influence of the early developing eye upon the origin of lens tissue is also clearly shown in experimentally produced cyclopic monsters (Mangold, 1930; Adelman, 1934; Stone and Dinnean, 1934) where the degree of fusion of the eyes determines the degree of fusion of the induced lenses. A complete fusion of two eyes into a single large median-placed one induces a single correspondingly large lens if contact is made with the surface ectoderm. If there is no contact, a lens fails to form (Stone and Dinnean, 1934).

When this lens is fully differentiated it is bathed in front by the aqueous humor, while the vitreous body lies just behind it. Its only direct connection with any cellular elements of the tissues which surround it are through

zonule fibers that hold it in place. Therefore, if the original lens is detached from these fibers and entirely removed from the eye, it would at first appear incredible that replacement of a lens could take place in any vertebrate eye when no trace of the original tissue remains behind as a source for regeneration.

REVIEW

Since most ophthalmologists may not be aware that this can occur, it may be of interest to review some of our recent experiments dealing with an unusual phenomenon which takes place in a small group of amphibian eyes.

In 1891, Colucci removed the lens along with some other tissues from the eyes of European salamanders and noted that a new lens developed in the eye by a budding process arising from the pigmented iris tissue along the dorsal pupillary margin.

This has been confirmed by different investigators since that time and up to now experiments by me have shown that it occurs in 14 species of salamanders, including those already reported. However, we have already found that there are many other species of these tailed amphibian forms which are unable to replace the lost lens as in other classes of vertebrates which have been tested.

How much evidence exists for lens regeneration among the salamanders' close relatives, the tailless amphibians, frogs and toads, is a debatable question at the moment. In fact it would be difficult to say how widely the potentiality for lens regeneration is hidden in the eyes of many vertebrates until far larger numbers of animals have been explored at various periods during development.

For recent reviews of the literature on this subject, reference is made to Stone and Sapir, 1940; Stone and Chace, 1941; Reyer, 1948 and 1950.

* From the Anatomical Laboratory, Yale University School of Medicine, and the Osborn Zoological Laboratory, Yale University. This study was aided by grants from the James Hudson Brown Memorial Fund of the Yale University School of Medicine and from the United States Public Health Service, National Institute of Neurological Diseases and Blindness, B-23 (C4).

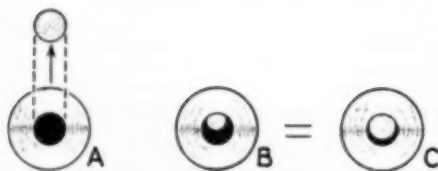


Fig. 1 (Stone). Schematic representation of operation and result showing removal of lens (A) followed by lens regeneration from pupillary margin dorsal iris (B) and further growth (C). All figures concern adult eyes of the newt, *Triturus viridescens*.

PRESENT KNOWLEDGE

We can summarize our present knowledge about the conditions under which a post-embryonic lens can come into existence by our experiments on the common American vermilion-spotted adult newt, *Triturus viridescens*. A motion picture film has been prepared to bring together these results.

As long as the original normal lens remains intact in this eye no other lens normally arises in its presence. If it is permanently removed, then it is replaced by a new one which develops from the dorsal pupillary margin of the iris (figs. 1 and 2 A-H).

If it is taken out and put back immediately or if the lens of another species is put in its place, lens regeneration is completely inhibited. However, if a severe cataract condition develops in the implanted lens, regeneration of another is released just as in the case of surgical removal.

We have also found in this species that, when the eye has been transplanted, a cataract develops which rapidly destroys the original lens. This is followed by lens regeneration from the dorsal iris (Stone and Chace, 1941). Mechanical factors, such as the size of the lens, its shape, or volume, play no role in inhibiting lens regeneration, for wax or glass spheres similar in size to a normal lens, as well as various types of tissues, when implanted into an eye immediately after the lens has been removed, do not restrict lens regeneration.

Therefore the removal of the lens from

the environment of the iris, which is normally a thin, black, pigmented membrane (fig. 2-A) is followed in about a week by a thickening of the iris and a depigmentation of its cells (fig. 2-B) along the free dorsal margin around the 12-o'clock position.

In a few more days, proliferation of the cells begins along the margin (fig. 2-C) and soon a vesicle is formed (fig. 2-D and E), the inner pole of which becomes polarized to

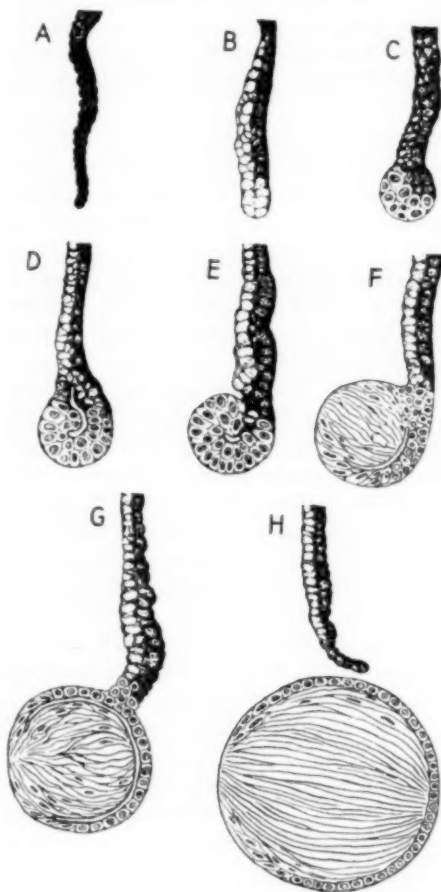


Fig. 2 (Stone). Drawing to show in cross section the regeneration of lens from the pupillary margin of the dorsal iris from 0 to 30 days after removal of the original lens. Normal iris (A); nine days (B); 12 days (C); 14 days (D); 16 days (E); 21 days (F); 25 days (G); and 30 days (H).

form the primary lens fibers, while the outer surface is devoted to the anterior sub-capsular epithelial layer (fig. 2-F).

In about 25 days after the removal of the original lens, the interior of the lens regenerate is being filled with the secondary lens fibers (fig. 2-G). At this time it is usually still attached to its source of origin, the dorsal iris. By the end of a month (fig. 2-H), the outer capsule completely surrounds the lens which then detaches itself and lies in the pupillary space.

The dorsal iris soon returns to its normal appearance and, by the end of a year, the size of the new lens reaches almost that of the original one (Stone and Chace, 1941).

If the lens regenerate at the time of its detachment is implanted in another eye immediately after a normal lens has been removed, the presence of the implant inhibits lens regeneration from the host dorsal iris to the same degree as a fully mature lens does. Implants of earlier lens regenerates do not have this inhibiting effect.

Two lenses can, however, develop side by side in the same eye. This is shown by an experiment where dorsal iris tissue from a normal eye is excised (fig. 3-A) and implanted in an eye immediately after the normal lens of the host eye is removed (fig. 3-B). Lenses regenerate simultaneously from both the implanted iris and the dorsal iris of the host eye (fig. 3-C).

If one of these lenses becomes cataractous and degenerates within the first three weeks of its development, lens regeneration is again

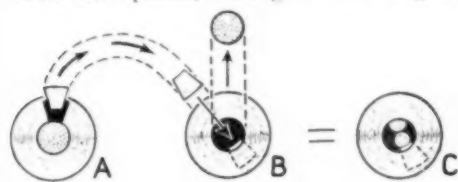


Fig. 3 (Stone). Schematic representation of operation and result showing normal dorsal iris excised (A) and implanted in another eye immediately after lens removal (B). Lenses develop simultaneously from both host dorsal iris and implant (C).

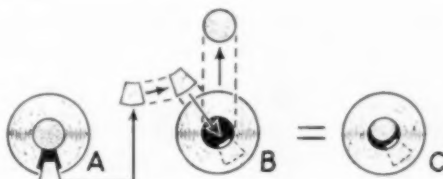


Fig. 4 (Stone). Schematic representation of operation showing normal ventral iris excised (A) and implanted in another eye immediately after lens removal (B). Ventral iris never develops lens, host dorsal iris always does (C).

released from the same dorsal iris tissue without inhibition from the surviving lens regenerate in the environment. However, older lens regenerates, 25 days or more in age, inhibit further lens regeneration in the same environment.

This fact was well established when lens regenerates at all ages were placed in eyes immediately after removal of the normal lens. Lenses developed normally from the host dorsal iris without inhibition in the presence of the implanted lens regenerate provided the latter was less than 25 days old (fig. 2-B to G).

Experiments show that, when the normal lens is removed (fig. 1-B), a new lens usually arises from the pupillary margin of the dorsal iris at the point around the 12-o'clock position. Many iris grafts taken from all regions of the dorsal half from the 9- to 3-o'clock positions and placed into lensless eyes show that the potency for lens regeneration gradually decreases to zero as one approaches the 9- and 3-o'clock positions. Below these points none of the ventral iris transplants give rise to lenses as indicated in a typical experiment in which ventral iris tissue is implanted into a lensless eye (figs. 4-A and B).

Only the host dorsal iris in such a case (fig. 4-C) is capable of responding to the conditions that can release lens regeneration. Somewhat similar results were found in experiments on the larval eyes of an European salamander by Sato (1933). This indicates that the cells capable of responding to lens

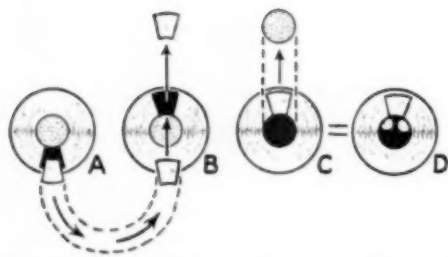


Fig. 5 (Stone). Schematic representation of operation and result showing nonlens-forming ventral iris excised (A) and replacing normal dorsal iris (B). Later when normal lens of host eye is removed (C) two lenses regenerate from dorsal iris tissue on either side of ventral iris graft (D).

formation lie in a somewhat restricted area in the eye.

One can take advantage of this fact and devise experiments which can further test the lens-forming capacity of the free pupillary margin of the dorsal iris and at the same time study the conditions under which multiple lenses might be formed simultaneously from dorsal iris tissue.

This is shown in an experiment where the nonlens-forming ventral iris tissue (fig. 5-A) is substituted (fig. 5-B) for a segment of dorsal iris. Later, when the normal lens is removed (fig. 5-C), two lenses regenerate from the dorsal iris tissue one on either side of the graft (fig. 5-D).

This is not due to any type of injury along the pupillary margin of the iris, for many control experiments showed that injuries, such as slits radiating from the pupillary margin of the iris upward toward the corneo-scleral junction, healed readily without stimulating lens formation.

In the experiments so far described, the lens regeneration has been released only along the pupillary margin of the dorsal iris tissue. Further experiments show, however, that the cells which have a capacity for lens formation are not confined to the free margin, but are distributed to other areas in the dorsal iris.

This can be revealed experimentally by producing secondary pupils in various regions of

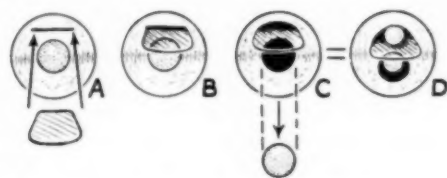


Fig. 6 (Stone). Schematic representation of operation and result showing slit in dorsal iris (A) for implanting small sheet of plicofilm (B). When secondary pupillary space forms normal lens is removed (C). A lens develops from dorsal iris tissue in both the primary and secondary pupils (D).

the dorsal iris through the insertions of pieces of plicofilm (fig. 6-A and B). When the wound in the dorsal iris is healed around the plicofilm making a permanent secondary opening, the normal lens is removed (fig. 6-C). Simultaneously a lens regenerates from the dorsal margin of the secondary pupil, as well as from that of the original one (fig. 6-D).

When the secondary pupils are gradually located nearer the ciliary margin of the iris, smaller lens regenerates appear until finally a line is reached where the presence of lens-forming cells are no longer revealed by this type of experiment.

All of the foregoing experiments show that the potentiality for lens regeneration is possessed by cells found over a wide area of the dorsal iris. The extent of this area is further indicated by another experiment in which a large section of the dorsal iris was removed leaving only a narrow rim of iris tissue at the periphery (fig. 7-A). The excised tissue was gradually replaced by re-

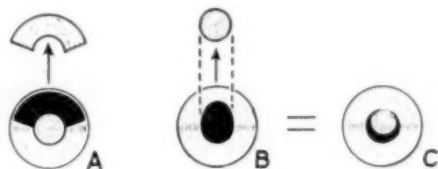


Fig. 7 (Stone). Schematic representation of operation and result showing lens-forming area of dorsal iris excised (A) and later when iris is partially regenerated the removal of the normal lens (B). Lens regenerates from regenerating dorsal iris (C).

generation and later, when the original surviving lens was removed (fig. 7-B), another lens regenerated from the dorsal pupillary margin of the regenerating iris (fig. 7-C) even before the latter was completely reformed. Therefore, cells remote from the original dorsal pupillary margin not only can replace by regeneration a large area of dorsal iris but they can restore the lens-forming ability to the cells in the new tissue.

How far beyond the ciliary margin of the dorsal iris tissue one can find pigmented epithelial cells which are capable of giving rise to lens tissue can only be revealed by further experimentation. However, as soon as we extend beyond this zone we invade an epithelial region devoted to the retina.

Before we consider proposals to test the cells in this portion of the eye, it should be pointed out that the retinal pigment cells of the adult salamander eye can give rise to all of the elements living above them—namely, the neural retina, which consists of the rod-cone elements, intermediate bipolar cells, ganglion cells, and intervening layers.

These retinal pigment cells can regenerate a new neural retina whether the latter is lost by degeneration (Stone, 1947 and 1950a), or by complete surgical removal (Stone, 1950b). Since the retina can be regenerated in these animals, it is possible to transplant functional eyes even between different species and later study returning vision (Stone and Zaur, 1940; Stone and Farthing, 1942; Stone, 1946).

Further tests have now been made of the activity of these pigment cells in many grafts of retinal pigment epithelium which, along with the underlying chorioid layer and sometimes the sclera, were placed in the aqueous chamber or pupillary space in lensless eyes. In a majority of the grafts, the retinal pigment epithelium gave rise to beautifully differentiated neural retinal membranes.

When the retinal pigment epithelium of the graft came from the dorsomedial wall of the eye, which was well isolated from and never connected with the iris tissue, there

were a few cases in which not only a well-differentiated neural retina developed but also a lens. The lens was seen to be attached to a margin of the graft, where the retinal epithelium extended like a thin membrane from the regenerated neural retinal portion as though it were reconstructing itself into a sheet of irislike tissue.

Apparently this layer of cells, in proliferating as a thin shelf beyond the body of the graft, lost ability to form neural retinal elements and took on lens formation instead. In our experiments, the conditions rarely appeared to be favorable in bringing forth the lens-forming capacity in these retinal pigment cells.

These results are of interest since it has recently been claimed by Sato (1951), working on a Japanese salamander, that retinal pigment epithelium could form lens tissue when implanted in a lensless eye.

We are, therefore, at the interesting stage of our explorations when we can say that the potentiality for postembryonic lens formation is masked in pigment cells not only in the iris but in the retina as well. The conditions under which lens regeneration becomes inhibited or released is of considerable importance from many biologic points of view.

We already have some important information which bears upon this part of the problem. Normally, the iris tissue is bathing in the aqueous humor which is also circulating around much of the surface of the lens and exchanging with the latter various chemical substances associated with lens metabolism.

Under these normal circumstances, in the presence of the lens, the dorsal iris tissue of the salamander eye never releases its capacity for lens regeneration. If, however, we insert a thin sheet of plicofilm into the eye (fig. 8-A) to wall off the dorsal iris in a chamber by itself so that it is not bathed by the aqueous humor which contacts the intact lens, the latter no longer exerts any inhibitory effect.

Lens regeneration is then released from the cells in the dorsal iris (fig. 8-B). This

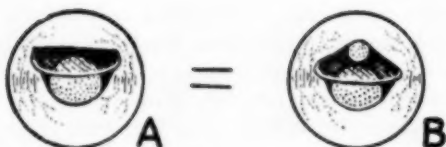


Fig. 8 (Stone). Schematic representation of operation and result showing implanted sheet of pliofilm isolating dorsal iris from lens and the aqueous humor bathing it (A). This releases lens regeneration from dorsal iris (B).

does not take place if the dorsal iris fails to be completely isolated by the artificial chamber.

The important role which the aqueous humor is playing in this whole problem is further shown when daily injections of aqueous humor from eyes containing lenses are made into eyes from which the lenses have been removed (fig. 9-A, B, and C). It was found by our experiments that lens regeneration could be inhibited for many weeks in this way.

Since daily injections of Ringer's solution in control eyes showed no inhibitory effects, it is apparent that the inhibiting factors are of a chemical nature floating in the aqueous humor around the living lens tissue (Stone and Vultee, 1949). Whether this is a specific factor or a combination of factors related to the metabolism of the living lens fibers is being further investigated.

It has been shown in the preceding experiments on the adult eyes of this *Triturus* salamander that the lens regenerates from the pupillary margin of the dorsal iris at about the 12-o'clock position when the normal lens is removed or when the dorsal iris is isolated from the lens by an artificial chamber.

The question now arises, how early in the development and under what circumstances does the future lens-forming area become polarized in this region of the eye?

The answer to part of this question is that it becomes polarized very early in embryonic development around the beginning optic-cup stage, long before the iris is formed. This was easily determined by first excising, rotating 180 degrees, and implanting embry-

onic eyes at various stages in development.

Later in the larval life of the hosts, the original lens was removed. We noted that in those cases in which the embryonic eye had been rotated before the approach of the optic-cup stage, the lens regenerated at or near the 12-o'clock position. Therefore, the position of the future lens-forming area had not become determined at the time of operation.

In all cases, however, in which the developing eye had been rotated during or subsequent to this critical stage, the regenerating lens arose at the 6-o'clock position. This demonstrated that the polarization had already taken place at the time the eye was rotated and that the dorsal iris was now reversed in position.

Our experiments furthermore indicate that the establishment of the future lens-forming area takes place at about the same stage in development as was described by Sato (1933) in another salamander. The determining factors which induce the polarization are not yet known, but it is quite possible that they arise from the developing brain against which the embryonic eye lies.

Although the future lens-forming region is determined early, its potentiality cannot be forced to reveal itself immediately. This was shown in our laboratory by experiments of Reyer (1950) on this species. The original presumptive lens ectoderm was removed early and substituted by grafts of tissue which prevented further lens inductions.

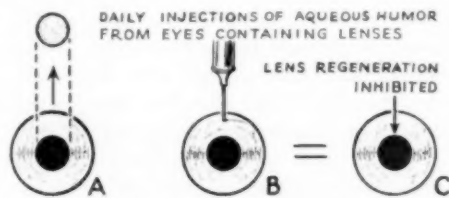


Fig. 9 (Stone). Schematic representation of operation and result showing lens removal (A) followed by daily injections of aqueous humor taken from eyes with normal lenses (B). Lens regeneration is inhibited for many weeks as long as injections are continued (C).

This was followed by an early temporary period when the eye continued development without a lens.

Even though an original lens was not allowed to develop in these eyes, this status did not prevent the further establishment of a mechanism for lens formation, for as soon as the iris developed from the margin of the optic cup a lens arose from the free edge of the dorsal iris in the usual place.

DISCUSSION

In the eyes which have been illustrated in the foregoing experiments it is possible to follow a chain of events that involves two forms of lens formation, which, when we have explored them more thoroughly, may prove to be more closely related than now appears on the surface.

At first the mechanism for lens formation expresses itself in the nature of some stimulus, perhaps of a chemical nature, that passes from the embryonic eye to the responding surface ectoderm with which it makes con-

tact. As the eye develops, the mechanism apparently becomes embodied within cells in the dorsal part of the eye and spreads into the dorsal iris when the latter forms. The lens-forming potentiality of the cells is then restrained from expressing itself by the presence of living lens fibers or by some substance produced by them.

One might conclude from present knowledge that, during early development when the eye loses its inductive influence for lens formation in the surface ectoderm, the second stage, which makes lens regeneration from eye tissue possible, is either completely lost in most vertebrate eyes or, if even feebly retained, its presence has not yet been unmasked by our studies.

This is a challenge to extend our knowledge further in a field of investigation in which the mechanism of lens regeneration can also be used as an unique tool applied to fundamental studies of cell dedifferentiation, proliferation, and differentiation.

Yale University School of Medicine.

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DISCUSSION

DR. JOHN BELLOWES (Chicago): It is interesting to note that not only the eyes of lower animals but even human eyes attempt lens regeneration. In the human eye, attempts to produce a new lens come from the lens capsule and epithelium. For example, after an extracapsular extraction, Elschnig's pearls may appear; each sphere represents a miniature crystalline lens.

In certain lower animals, the destruction of the optic vesicle in embryonic life results in aphakia.

Even in man, it is likely that some stimulus from the optic vesicle or the retina is necessary for the integrity of the lens and, in the absence of this stimulus, the lens undergoes degeneration and forms a cataract. This is the possible explanation for the origin of cataracta complicata which occurs in the diseases of the posterior segment.

I wish to ask Dr. Stone whether destruction of the posterior half of the eye was attempted in his experimental regeneration and if the lens was still able to appear from the dorsal iris.

DR. LEON S. STONE: I might say that we have discussed in other publications the question whether a lens will form in the absence of retinal tissue.

I believe the retina is playing a part in the total picture of the regeneration of the lens. We have transplanted pieces of the dorsal iris tissues to the body cavity where the early stages of lens regeneration have taken place from the grafts isolated from the retina. However, they merely develop into small lentoids which never progress very far in growth. As I have pointed out in the essay, one can study the development of cataracts in such experiments as these.

I don't know how many of you are familiar with the development of the marsupials. The opossum is the only example we have on this continent. I would like to point out that at birth its eye is in the same stage of development as that of a five-week-old human embryo. At this time, the lens is in a late vesicle stage of development and it should present an unique opportunity to study experimentally the early development of various types of cataracts.

DR. DAVID G. COGAN (Boston): As Dr. Bellowes stated, there does seem to be an unsuccessful attempt in the human eye to regenerate lenses or something that simulates lenses.

Along that line, it would be interesting to fractionate Dr. Stone's inhibitory factor, for example,

to remove most of the lens, leaving the epithelium intact, and see if the epithelium of the lens inhibits it, or whether it is something from the cortex.

I have certain qualms about the interpretation of Dr. Stone's experiments. I think we should emphasize the fact that Dr. Stone does not feel he has discovered any method by which lenses may be regenerated in human beings. That has professional implications, Dr. Stone, which might be unfortunate.

DR. HERMANN M. BURIAN (Iowa City, Iowa): At what time does the regenerated lens become clear? Is it clear from the beginning? At what point does it become transparent?

DR. STONE: If one examines the gross specimens under ordinary light conditions under the microscope from the time the vesicle begins to appear, a bluish-gray structure can be seen growing down from the free margin of the dorsal iris. Not until the inner portion of the regenerating lens vesicle is filled with the primary lens fibers does it begin to be transparent. As soon as the equatorial zone gives rise to the secondary lens fibers, one can then observe quite a clear lens.

DR. LUDWIG VON SALLMANN (New York): I don't know whether I understood Dr. Stone correctly, but I believe he said that he identified two conditions which inhibited regeneration of the lens from the dorsal iris; one of these was the presence of a completely formed lens capsule, and the other was repeated injection of normal aqueous continued for 90 days.

I should like to know then whether Dr. Stone feels that it is the lens capsule or the lens epithelium that is the factor in this inhibition. Secondly, I should like to ask whether controlled experiments have been carried out in which Ringer's solution was injected for 90 days.

DR. STONE: We continued our injections of Ringer's solution until a large lens-regenerate appeared in the eye. I do not recall that we carried them on for as long as 90 days. However, 60 days were long enough to prove that mere introduction of a needle, or the mere injection of Ringer's solution, or the withdrawal of aqueous humor already in the eye, did not interfere with the release of lens regeneration nor the growth of the lens regenerate.

As far as the completion of the capsule is concerned, as well as the role it plays in early lens

regeneration, I can only say that the full development of the capsule coincides with the moment when the lens regenerate separates itself from its source of origin, the dorsal iris.

From what we know about the general physiology of the lens, I would assume that a lens regenerate at the time it is detaching itself from its source of origin, has reached the point at which its membrane has already become functional and anaerobic metabolism becomes the mechanism governing the nourishment that had previously come in along the epithelial attachment with the iris.

As far as the epithelium is concerned, do you mean the subcapsular epithelium? The subcapsular epithelium is established very early in a regenerating lens, and in the early stages when there is a large capsule (because it is still growing) its cells do not inhibit regeneration of lens from other dorsal iris tissue.

I think it might be a combination of many metabolic agents that are given off by the living mature lens which keeps the iris cells in equilibrium and inhibit regeneration. That may involve a biologic principle which might apply to other forms of regeneration.

There is nothing specific flowing in the blood stream either through the presence or absence of an eye on the other side. If only one lens is removed, regeneration takes place in the normal fashion. If there is no lens in either eye, complete lens regeneration will take place in both eyes.

DR. V. EVERETT KINSEY (Detroit): Dr. Stone—

have you made any attempt to fractionate the substance which is inhibitory? For instance, is it heat labile, or do you know anything about its nature?

DR. STONE: No. I have not done it so far, but I am hoping that one of my graduate students will take up this problem.

DR. LAWRENCE DAME (Greenfield, Massachusetts): Dr. Stone, do you have any estimate as to the optical efficiency of this new lens?

DR. STONE: Regarding vision in these animals with new lenses I can cite the results of many of our experiments on transplanted eyes, which will be taken up in another paper.

I have always found that, when an eye is taken out, for example, and transplanted, not only the retina but the lens as well degenerates in these animals. In three months' time the neural retina regenerates from the pigment cells, and an optic nerve grows back to the brain. The regenerated lens from the dorsal iris is quite small at this time but it fills the entire pupillary space.

When we tested for vision before and after the transplantation of the eyes by means of rotating drums with various widths of alternating black and white stripes, we found that visual acuity gradually became as sharp as it was in the beginning before operation. That was about five or six months after operation. So, I would say, the new lens is giving good service.

THE IN VITRO REVERSAL OF THE LENTICULAR CATION SHIFT INDUCED BY COLD OR CALCIUM DEFICIENCY*

JOHN E. HARRIS, M.D., LETA B. GEHRITZ, M.S., AND LORETTA NORDQUIST, B.A.
Portland, Oregon

The lens, like most tissues, normally maintains a high potassium and low sodium concentration, even though bathed in a fluid high in sodium and low in potassium. Under certain conditions, notably developing cataract, there occurs what might be termed a degradation of the cation content, that is, a shift toward equilibrium, potassium leaving the lens and sodium entering.¹ This shift is generally considered to result from death of the cell and to be irreversible.

Of interest is the fact that this cation degradation can be readily duplicated in vitro under circumstances not necessarily associated with cell death. When the metabolic intensity of the rabbit lens is lowered by refrigeration, treatment with metabolic poisons or deprivation of glucose, it loses potassium and gains sodium.²

The cation shift can also be produced by alteration of the permeability of the limiting lenticular barriers, probably cellular membranes. Thus, either a decrease in the energy output by the lens or an increase in the permeability of its barriers is followed by a shift in cation toward equilibrium with the extracellular fluid.

* From the John E. Weeks Memorial Laboratory, Department of Ophthalmology, University of Oregon Medical School. Supported in part by a grant from the Diabetic Research Foundation, Portland, Oregon, and the U. S. Public Health Service.

In view of these considerations, it is important to know whether the shift in the cation content induced by deviations from the usual environment can be reversed when relatively normal conditions are reestablished. The reversal of a cold-induced cation shift has been demonstrated in the human erythrocyte³ and the retina⁴ and can be reasonably anticipated in the lens if the concept, advanced in a previous publication,² of an active transfer of cations across lenticular barriers is correct.

Extension of such studies to include the effect of various metabolites and metabolic processes on the cation content and reversal of the cation shift would contribute to a better understanding of the mechanism which normally maintains the cation distribution. Moreover, it is reasonable to assume that the cation shift seen in developing cataract reflects the breakdown in the metabolic processes which ultimately leads to an opacity.

These studies should, therefore, increase our knowledge of the pathogenesis of cataracts and supply direction to efforts to prevent or reverse the cataractous change.

We have, accordingly, undertaken to determine whether the induced cation shift can be reversed, to study the kinetics of the reversal if possible, and thus to lay the ground work for future studies of various influential metabolic factors. As test procedures, we have sought to reverse the cation shift induced by cold and by calcium deficiency.

EXPERIMENTAL

As part of our previous studies, we attempted to reverse the cold-induced cation shift by raising to 37°C. the temperature of a lens bathed in 15 ml. of Tyrode's solution. This failed.

As a point of departure in the present studies, therefore, certain changes in the medium and technique were made: *First*, the potassium concentration of Tyrode's solution was increased to 5.0 milliequivalents per liter, the level normally found in the rabbit's aqueous.

Second, the bicarbonate concentration was

increased to 23.8 mEq./liter, a concentration which more closely approximates that of the rabbit's aqueous. This increased the buffer capacity and permitted a reduction in the volume of the bathing medium to a minimal quantity (3.0 ml.); employment of a minimal extracellular volume was found by one of us (J. E. H.) to be desirable in similar experiments on the erythrocyte.

As in our previous studies, we increased the glucose content from 150 to 200 mg. percent to insure an adequate supply of nutrient material. The resulting solution constituted the basic medium and is referred to as modified Tyrode's solution. Further alterations (addition of glutamic acid or removal of calcium) were made as indicated.

To maintain osmotic constancy, all alterations in Tyrode's solution were compensated by the subtraction or addition of an equivalent amount of sodium chloride. When calcium was deleted from the medium, the final sodium concentration was 150 mEq./liter; in all other solutions the concentration was 148 mEq./liter.

The procedure otherwise has been previously described² and is only briefly reviewed. Rabbit eyes were enucleated and the lenses extracted by turning back the sclera, removing the vitreous, and cutting the zonules. Generally, lenses weighing between 0.250 and 0.400 gm. were used, although an occasional lens over that limit was included. (Our data does not permit a conclusion concerning the effect of the age or size of the lens on the results observed.)

Each lens, resting on its posterior surface, was submerged in 3.0 ml. of solution, overlaid with a mixture of 5.0-percent CO₂ and 95-percent O₂ in a small tube, tightly stoppered. Aseptic techniques were employed throughout.

After the appropriate procedure, the lens was removed, weighed immediately, dried at 105°C. for 48 hours, ashed, and the sodium and potassium content determined on a Perkin-Elmer flamephotometer, using lithium as an internal standard. The pH of the media and the glucose content were de-

terminated before and after each experiment. The method of Somogyi⁵ was used for determining glucose.

Ideally, such studies would be made by serial analyses of the same sample of tissue. This is not possible when the lens is the experimental structure. Thus, in the presentation of the data, comparison is always made between a group of lenses which serve as controls (which, depending upon the study, may be fresh lenses, refrigerated lenses or those incubated in media without calcium) and an experimental group which is subjected to an additional procedure.

Normally, the cation concentrations agree closely from lens to lens particularly when a comparison of the two lenses from the same animal is made. However, the potassium and sodium concentrations of refrigerated lenses were found to vary from animal to animal and from lens to lens of the same animal. This was also observed in lenses incubated at 37°C. in media containing no calcium.

Since the controls in these instances vary, a statistical analysis was found valuable.* Although not absolutely necessary, we have for the most part used one lens of a pair from the same animal as a control, largely because variation which might occur from certain other factors is thereby minimized.

REVERSAL OF THE COLD-INDUCED CATION SHIFT

A reduction in metabolic intensity is readily produced by refrigeration and easily reversed by raising the temperature. Our experimental approach, therefore, was to refrigerate the lens in an ice bath at 0°C. for 16 to 22 hours using modified Tyrode's solution as the bathing medium. At the end of this time one lens of a pair from the same animal was analyzed immediately while the other was placed in a water bath and incubated at 37°C. for a variable period before

an analysis was made.

The results of experiments of this type are given in Table 1. The loss of potassium and gain of sodium by the lens which occurred during refrigeration at 0°C. were reversed by simply increasing the temperature to 37°C. Potassium reentered and sodium left the lens; the movement in both cases was against a concentration gradient. Neither change could be accounted for on the basis of alteration in water content. The changes were statistically significant.

The ultimate goal would be the restoration of normal cation concentrations. Thus the significant measurement is the concentration at any time, rather than the change as measured by the actual difference in concentration between the incubated and the control lens. For example, a lens which has lost and regained potassium in the amount of 50 mEq./1,000 gm. of water is not necessarily a more active specimen than one which has lost and regained only 25 mEq./1,000 gm. of water, since both have returned to their initial level.

In Figures 1 and 2 the cation concentration is plotted against time of incubation of previously refrigerated lenses. The value at zero hours is the mean of the concentrations of the control lenses (that is, those subjected to refrigeration only).

Although the uptake of potassium and excretion of sodium are definite, the spread of the data is too great to determine the

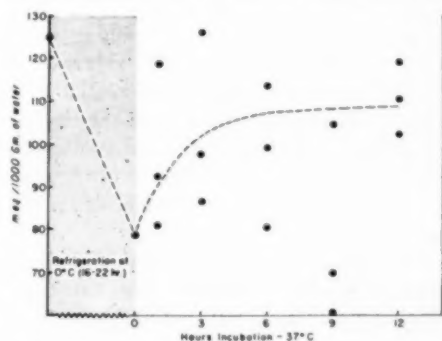


Fig. 1 (Harris, Gehrsitz and Nordquist). Accumulation of potassium during incubation of the previously refrigerated rabbit lens. (Medium—modified Tyrode's solution.)

*The t-test for significance was employed throughout; the mean of the control analyses was compared with the mean of the analysis obtained after the experimental procedure, accepting P equal to 0.05 as the level of significance.

TABLE 1
CHANGE IN CATION CONCENTRATION DURING INCUBATION OF THE PREVIOUSLY
REFRIGERATED RABBIT LENS
(Medium—Modified Tyrode's solution)

Hours Incubation	Potassium—mEq./1,000 gm. Water			Sodium—mEq./1,000 gm. Water		
	Control Lens 0°C.	Incubated Lens 0°C. + 37°C.	Change during Incubation	Control Lens 0°C.	Incubated Lens 0°C. + 37°C.	Change during Incubation
1	84.1 80.8 100.1	80.7 92.3 118.6	- 3.4 +11.5 +18.5	65.6 69.8 65.9	73.6 59.3 49.4	+ 8.0 -10.5 -16.5
3	85.3 73.1 112.3	97.4 86.2 126.0	+12.1 +13.1 +13.7	64.3 84.4 47.6	56.5 67.3 41.4	- 7.7 -17.1 - 6.2
6	73.4 82.5 44.7	80.8 113.8 98.8	+ 7.4 +31.3 +54.1	77.5 67.0 115.8	75.1 33.7 56.7	- 2.5 -33.3 -59.1
9	65.5 56.2 61.4	60.7 70.2 104.3	- 4.8 +14.0 +42.9	92.9 98.9 57.6	100.8 88.5 68.9	+ 7.9 -10.4 -38.9
12	94.8 81.7 80.8	102.8 110.2 119.0	+ 7.4 +28.5 +38.2	58.2 81.2 68.7	54.9 63.9 46.4	- 3.3 -17.3 -22.3
Mean S.D.	78.4 ±17.2			77.0 ±18.0		

kinetics of the shift with any certainty, although an approximation to an exponential function, as indicated by the dotted line, seems likely.

EFFECT OF *L*-GLUTAMIC ACID ON THE COLD-INDUCED CATION SHIFT

Having established that the cation shift which is induced by refrigeration can be reversed by warming the lens to 37°C., we turned our attention to determining more accurately the kinetics of this reversal. A knowledge of the kinetics is essential to a more thorough understanding of the mechanisms which maintain the cation concentrations; it is also essential for future studies of the effect of various procedures on the cation exchange.

The spread of the data obtained when modified Tyrode's solution was employed suggested that some metabolic adjuvant was lacking. Glutamic acid is known to enhance the uptake of potassium by the retina⁴ and was, accordingly, tried here. *L*-glutamic acid

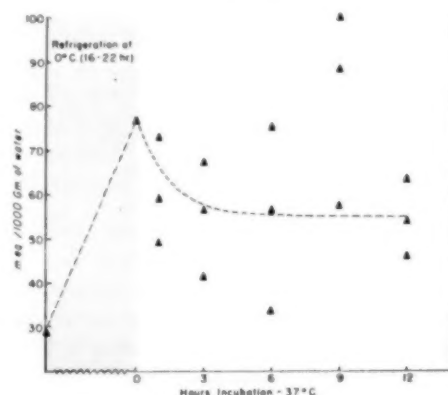


Fig. 2 (Harris, Gehrsitz and Nordquist). Excretion of sodium during incubation of the previously refrigerated rabbit lens. (Medium—modified Tyrode's solution.)

was added to the basic medium in sufficient quantity to achieve a final concentration of 0.01 M. Rabbit lenses were placed in this solution, refrigerated and subsequently analyzed immediately or incubated for variable

TABLE 2
CHANGE IN CATION CONCENTRATION DURING INCUBATION OF THE PREVIOUSLY
REFRIGERATED RABBIT LENS

(Medium—Modified Tyrode's solution with 0.01 M. *L*-glutamic acid)

Hours Incubation	Potassium—mEq./1,000 gm. Water			Sodium—mEq./1,000 gm. Water		
	Control Lens 0°C.	Incubated Lens 0°C. +37°C.	Change during Incubation	Control Lens 0°C.	Incubated Lens 0°C. +37°C.	Change during Incubation
1	104.6	114.0	+ 9.4	45.6	41.2	- 4.4
	82.0	102.7	+20.7	78.2	66.2	-12.0
	90.7	113.1	+22.4	60.4	45.4	-15.0
3	108.5	121.8	+13.3	43.4	34.3	- 9.1
	98.5	127.5	+29.1	60.4	47.1	-13.3
	91.0	125.2	+34.2	68.6	28.8	-39.8
6	105.8	125.4	+19.6	41.9	30.9	-11.0
	94.6	123.6	+29.0	63.6	36.4	-27.2
	76.6	120.2	+43.6	81.4	33.8	-47.6
9	111.4	112.0	+ 0.6	42.8	50.8	+ 8.0
	97.3	129.7	+32.4	66.6	35.0	-31.6
	80.2	117.5	+37.3	73.7	40.0	-33.7
	52.6	133.1	+80.5	109.9	41.0	-68.9
12	102.9	103.8	+ 0.9	51.5	61.8	+10.3
	84.7	108.5	+20.8	70.3	54.6	-15.7
	98.3	134.0	+35.7	58.5	23.6	-34.9
Mean	93.1			62.5		
S.D.	±15.1			±17.6		

periods before analysis as described above. The results are presented in Table 2.

A statistically significant uptake of potassium and excretion of sodium by the lens were noted during incubation. The outstanding finding was the marked tendency to return to the initial, that is, normal levels. (The average of 28 analyses of normal rabbit lenses for potassium was 124.6 mEq./1,000 gm. water with a standard deviation of ± 2.5 and for sodium was 28.2 mEq./1,000 gm. water with a standard deviation of ± 7.0). The potassium concentration reached the normally observed value at three hours. The sodium level approached but seldom achieved the normal level.

Beyond six hours' incubation, the potassium levels appeared to take divergent paths. A certain number (about one half) of the lenses continued to concentrate potassium, achieving values well above the normal range. In the remainder a gradual diminution of the potassium concentration and a simul-

taneous increase in the sodium concentration occurred. This was not surprising since a static medium was used and eventual metabolic failure should occur, although the time of onset would reasonably vary from lens to lens. These apparently secondary changes are indicated by dotted lines in Figure 3.

The kinetics of the uptake of potassium demonstrated a satisfactory approximation to the first order equation, $dC/dT = k(C_1 - C_t)$ where C_1 is the normal concentration, C_t the concentration at any time, T , and k is a proportionality constant which measures to a certain extent the ability of the lens in the particular medium to reestablish normal cation relationships.*

* Other expressions can be derived in which the change in concentration can be represented as a function of the permeability of the membrane and the active transfer mechanism. However, the data presented here would not permit a calculation of the individual functions. Our main concern at the moment is the effect of both processes acting together which is embodied in k .

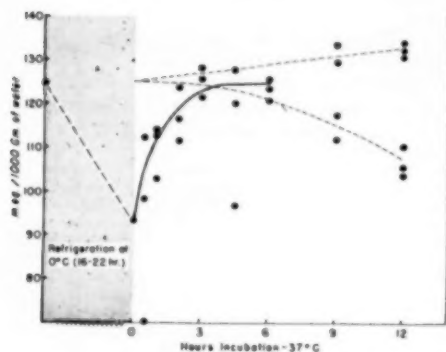


Fig. 3 (Harris, Gehritz and Nordquist). Accumulation of potassium during incubation of the previously refrigerated rabbit lens. (Medium—modified Tyrode's solution with 0.01 M. l-glutamic acid.)

Precise conformity cannot be expected since the lens volume did not remain constant. If the reestablished steady-state is not the original (normal) concentration, the equation must be modified to reflect this fact.

From the above considerations it is apparent that the degree of recovery of the normal value provides the best measure of the effect of various substances on the reversal of the cation shift. A convenient and satisfactory index for such studies can be obtained by calculating the percent recovery as is done in Table 3.

Since the normal value under optimal con-

ditions is reached at three hours, calculation of the percent recovery should be made at or near this time. It will be noted that as the percent recovery reaches 100, any error introduced by virtue of a variable base line reduces to zero. It is obvious, too, that a more satisfactory comparison is made with potassium than with sodium.

REVERSAL OF THE CATION SHIFT OBSERVED IN CALCIUM-FREE SOLUTIONS

Having shown that the cation shift induced by a lowered metabolic intensity is readily reversed by the simple expedient of raising the metabolic rate, we investigated the reversibility of the shift produced by an alteration in permeability.

It is known that calcium in the external medium markedly influences the permeability of animal membranes; when this ion is absent permeability is increased, and when it is present the permeability is decreased. The cation shift observed in the absence of calcium can be provisionally considered to be due to an increased permeability of the limiting lenticular barriers rather than to an altered metabolism.*

Two lenses from the same animal were

* This may not be true. Weekers* contended that lenticular glycolysis requires calcium. We observed no difference in the rate of utilization of glucose in modified Tyrode's solution with and without calcium.

TABLE 3
EFFECT OF GLUTAMIC ACID ON RECOVERY OF NORMAL POTASSIUM AND SODIUM CONCENTRATIONS DURING INCUBATION OF THE PREVIOUSLY REFRIGERATED RABBIT LENS

Hours Incubation	Potassium % Recovery (Mean)*		Sodium % Recovery (Mean)*	
	Without Glutamic Acid	With Glutamic Acid	Without Glutamic Acid	With Glutamic Acid
1	41	53	33	34
3	53	97	45	75
6	42	93	45	85

$$* \frac{(C_t - C_0)}{(C_i - C_0)} \times 100$$

Where: C_t = Concentration at any time T (incubation)
 C_0 = Concentration after refrigeration
 C_i = Initial concentration

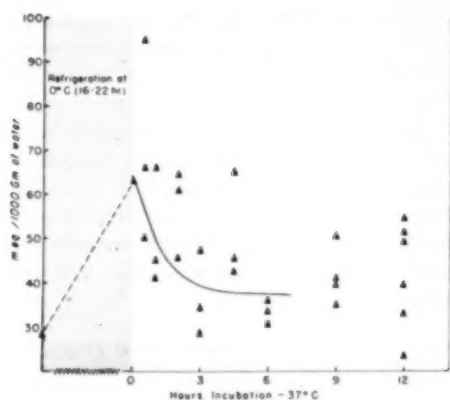


Fig. 4 (Harris, Gehrsitz and Nordquist). Excretion of sodium during incubation of the previously refrigerated rabbit lens. (Medium—modified Tyrode's solution with 0.01 M. *l*-glutamic acid.)

allowed to incubate at 37°C. in modified Tyrode's solution containing 0.01 M. *l*-glutamic acid but no calcium. After six hours, one lens was analyzed. Sufficient calcium to produce a final concentration of 10 mg. percent was added to the medium surrounding the other lens and incubation continued.

The results are graphically represented in Figure 5. They indicate, beyond question, that the cation shift induced when the lens

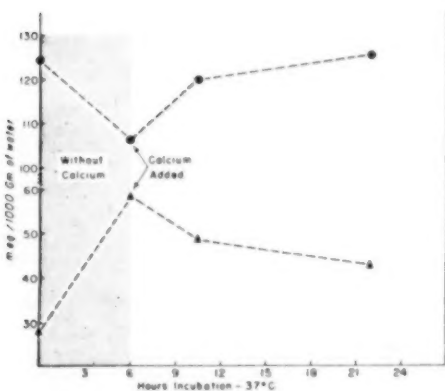


Fig. 5 (Harris, Gehrsitz and Nordquist). Cation shift induced by calcium deficient medium and its reversal when calcium is added. The circles represent potassium, the triangles sodium.

was incubated in a medium devoid of calcium was reversed when the calcium was added.

ACCUMULATION OF POTASSIUM AND SODIUM BY THE RABBIT LENS DURING INCUBATION AT 37°C.

As a result of incubation subsequent to refrigeration, a lenticular potassium concentration in excess of the normal level was occasionally observed (see fig. 3). To study this concentrating effect better, a series of experiments was performed in which one of a pair of rabbit lenses was analyzed immediately upon extraction and the other incubated at 37°C. (without prior refrigeration) for a variable period of time in modified Tyrode's solution with or without glutamic acid. The results are shown in Figures 6 and 7.

Here the difference between the concentration of potassium in the initial and in the incubated lens is plotted against time. During incubation, a concentration of potassium in excess of the initial value was achieved. Indeed, a 20-percent increase above the *in vivo* level was occasionally observed. The uptake of potassium was linear with time.

As in the previously cited experiments an

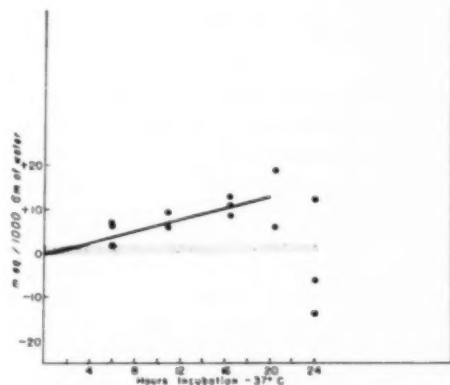


Fig. 6 (Harris, Gehrsitz and Nordquist). Accumulation of potassium during incubation of the fresh rabbit lens. (Medium—modified Tyrode's solution.) The thickness of the shaded base line at 0.0 concentration represents the average difference in concentration of potassium between the two lenses of the same animal.

occasional decrease in the potassium concentration was noted, reflecting again the fact that a static medium was used. Trauma resulting from extraction and handling of the lens may also have contributed to these occasional failures. A similar increase in potassium concentration above the *in vivo* level has been noted in erythrocytes incubated at 37°C.⁷

The sodium concentration was found to increase, also. The net result was, therefore, a rise in the concentration of total base in the lens, an increase which reached considerable proportions. (The average total base after 16 to 24 hours' incubation in media containing *l*-glutamic acid was 171.6 mEq./1,000 gm. of water). This result concurs with our observation that the decrease in concentration of sodium during incubation following refrigeration of the lens was somewhat less than the increase in potassium concentration (figs. 3 and 4).

It is to be admitted that an osmotic disparity between the bathing medium and any individual lens may have accounted for the increased concentration of base. However, the character of the curve substantially nulli-

fied any possibility that this was the *modus operandi*, since the increase in potassium concentration continued over a period of 24 hours.

Experiments with deuterium oxide have demonstrated that simple osmotic equilibrium should be achieved within the first few hours.⁸ Moreover and of greater significance, an absolute increase in the potassium and sodium content of the individual lens was observed (table 4).

CHANGES IN THE HYDRATION OF THE LENS

In addition to the shift in cations an uptake of water is noted when the metabolic intensity of the lens is lowered or the permeability of its limiting barriers increased.² This is attributable to the colloid osmotic pressure of the lens, which becomes increasingly manifest when the limiting cellular barriers are freely permeable to the anions and cations of the bathing medium, providing there is no compensatory active transfer mechanism. If this concept of swelling is correct, a signifi-

TABLE 4

CHANGE IN CATION CONTENT DURING INCUBATION OF THE FRESH RABBIT LENS
(Medium—Modified Tyrode's solution with 0.01 M. *l*-glutamic acid)

Hours Incubation	Microequivalents/Lens		
	Potassium	Sodium	Total Base (K ⁺ +Na ⁺)
3	+0.0	- 0.3	-0.3
	+0.4	+ 0.6	+1.0
6	+0.4	- 0.5	-0.1
	+1.2	+ 1.1	+2.3
11	+1.0	- 0.1	+0.9
	+0.9	+ 2.4	+3.3
16½	+0.8	+ 0.5	+1.3
	+3.2	+ 1.6	+4.8
	-1.8	+ 2.7	+0.9
20	+2.9	+ 1.9	+4.8
	+2.0	+ 4.8	+6.8
24	+1.1	- 0.4	+0.7
	+2.3	- 0.3	+2.0
	+1.4	- 2.7	-1.3
	-6.0	+13.2	+7.2

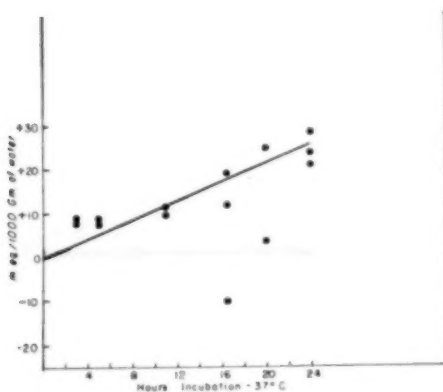


Fig. 7 (Harris, Gehrsitz and Nordquist). Accumulation of potassium during incubation of the fresh rabbit lens. (Medium—modified Tyrode's solution with 0.01 M. *l*-glutamic acid.) The thickness of the shaded base line at 0.0 concentration represents the average difference in concentration of potassium between the two lenses of the same animal.

TABLE 5
CHANGE IN CATION AND WATER CONTENT DURING INCUBATION OF THE PREVIOUSLY
REFRIGERATED RABBIT LENS

(Medium—Modified Tyrode's solution with 0.01 M. *L*-glutamic acid)

Hours Incubation	Microequivalents/Lens			mg./Lens
	Potassium	Sodium	Total Base (K ⁺ +Na ⁺)	Total Water
1	+ 2.7	- 3.2	-0.5	-13.4
	+ 3.4	- 3.2	+0.2	- 7.8
	+ 1.4	- 1.0	+0.4	- 3.2
3	+ 5.3	- 7.6	-2.3	- 8.2
	+ 1.9	- 2.2	-0.3	- 7.1
	+ 5.0	- 3.1	+1.9	- 6.9
6	+ 8.5	-10.7	-2.2	- 8.2
	+ 5.4	- 5.7	-0.3	+ 3.2
	+ 3.4	- 2.0	+1.4	- 0.5
9	+ 7.5	- 9.2	-1.7	-16.9
	+13.7	-16.7	-3.0	-31.1
	+ 6.0	- 6.6	-0.6	- 5.0
	+ 2.1	+ 1.8	+3.9	+11.7
12	+ 4.7	- 6.0	-1.3	- 9.3
	+ 6.1	- 5.4	+0.7	- 6.4
	+ 0.9	+ 2.2	+3.1	+ 5.1

cantly higher content (not concentration) of total base should be demonstrable in the swollen lens. This has been observed.

With the reestablishment of normal metabolic relationships, for example, raising the temperature after refrigeration, a decrease in the total base content and a dehydration of the individual lens was noted (table 5). However, not infrequently a rise in the total base was accompanied by a decrease in the water content per lens.

This was observed even more strikingly in the lenses incubated without prior refrigeration. Here an increase in total base and a decrease in water content was the rule. We have tentatively concluded that the hydration of the lens is due not only to a balance of osmotic forces (as measured by the summation of changes in total potassium and sodium) but also to some other factor. This other factor appears to be influenced by the metabolism of the cell.

Those procedures which promote an accumulation of potassium and excretion of sodium also favor a dehydration of the lens even though there is a concomitant increase

in the content of total base. Conversely, a decay of certain processes leads to a loss of potassium, a gain of sodium, an increase in total base, and lenticular hydration. A thorough analysis of this process is not germane to the present thesis and will be presented in a future publication.

DISCUSSION

When radioactive potassium and sodium are injected into the normal animal they readily find their way into the lens.⁹⁻¹¹ Thus, the lens barriers (the capsule and cellular membranes) are normally permeable to the positive ions.* The concept has been advanced, therefore, that any particular steady-state represents a balance between an active transfer mechanism which tends to concentrate potassium within and sodium without the cell and a passive diffusion which permits movement in the reverse direction along a concentration gradient. Our results substantiate this concept in detail.

First, an active transfer mechanism has been demonstrated.

Second, reversible alteration of this active

transfer process and of the permeability of the barriers has been shown to induce a reversible cation shift.

Third, the kinetics of the uptake of potassium, and of the excretion of sodium measured during incubation of the previously refrigerated lens, fit the concept.

It has been suggested that the active transfer mechanism in the erythrocyte¹² and possibly other cells¹³ is limited to the excretion of the sodium ion, potassium accumulating to maintain electrical neutrality. If such is the case, one would predict that, with certain obvious exceptions, changes in the potassium and sodium content should be in opposite directions, that is, if potassium decreased, sodium would increase and vice versa. However, we noted an increase in both the potassium and sodium content when the fresh lens was incubated at 37°C.

This might suggest that there are two

* There is little reason to doubt that the lens fibers normally contain sodium.

First, the total sodium space that can be calculated from our data (13 percent of the lens volume) is greater than the chloride space (8.7 percent) measured by Langham and Davson.¹⁰ (The finding of a higher sodium than chloride space is not unexpected.) A certain amount of chloride is probably intracellular; the cellular concentration of sodium is still higher.

Second, the demonstration of an active transfer of sodium and a reversible sodium shift provides presumptive evidence that the lenticular fibers contain this ion.

Langham and Davson¹⁰ calculated a "readily-available space" of the rabbit lens from the distribution of Na^{24} between the lens and aqueous in vivo and found it to be less than the chloride space. Thus, within the time limit of their experiments radioactive sodium did not exchange with all the sodium of the lens.

This does not of necessity indicate that the fiber membranes are impermeable to sodium. Rather, the results emphasize the fact that exchange equilibrium between the lens and bathing medium must be very slow to obtain.

The results of von Sallmann and Locke¹¹ with K^{40} show the same lack of exchange equilibrium with respect to potassium.

Parenthetically, it should be noted that our analyses represent only the average composition of the entire lens, including an extracellular fluid of uncertain volume and composition. Probably our experimental procedures produced more profound changes in the superficial than in the central fibers.

active transfer mechanisms, one for potassium and one for sodium, which are usually influenced by the same metabolic factors but which are capable of independent activity. More logically, however, such an increase in total base can be attributed to an accumulation within the lens of an acid ion, for example, a product of cellular metabolism. In addition, the increase in lenticular sodium, in particular, could result from an increased extracellular volume.

Consequently, the data presented provides no basis for concluding whether one or both cations are actively transferred. The concept of a cation pump superimposed on a permeable membrane is a convenient generalization that follows reasonably well from our present knowledge and provides a point of departure for future studies. However, extension of this concept to more detailed conclusions concerning the events that transpire across the lenticular barriers is not possible at the moment.

It seems reasonable to assume that the loss of potassium and gain of sodium by the lens during developing cataract represents either a decrease in the active transfer mechanism or an increased permeability of the cellular barriers or both. It is equally reasonable to conclude from the data here presented that the cation shift observed in cataract formation may be reversible, at least in the early stages.

SUMMARY

1. The loss of potassium and gain of sodium which are observed when the metabolism of the lens is decreased by refrigeration were found to be reversible when the temperature of the lens was raised to 37°C., potassium re-entered the cell and sodium was excreted from it.

2. Glutamic acid enhanced the accumulation of potassium by and excretion of sodium from the previously refrigerated rabbit lens during incubation at 37°C. The kinetics of the cation shift were determined.

3. The cation shift toward a true equilib-

rium induced in a calcium deficient medium was reversed when calcium was added.

4. A gradual increase in the concentration of potassium and sodium by the lens was noted during incubation of the fresh lens. This was due to both an increase in the total amount of cation and a dehydration of the lens.

5. The results confirm the current concept

that any cation ratio is a balance between two opposing movements of cation, one against a concentration gradient which is due to an active transfer mechanism and the other with a concentration gradient representing a passive movement through normally permeable barriers.

3181 S.W. Marquam Hill Road (1).

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DISCUSSION

DR. JONAS S. FRIEDENWALD (Baltimore): I am sure Dr. Harris is familiar with the modern work that has indicated that potassium accumulation is related in many instances to organic phosphates within the cells in which the potassium is accumulated. That has been shown on the red cells and on the colon bacillus and also recently by Dr. Ling, in our laboratories, on the retina.

I wonder whether Dr. Harris has done any studies on organic phosphate in the lens in relation to potassium accumulation.

DR. HARRIS: No, we haven't Dr. Friedenwald, but that certainly is indicated. The accumulation of potassium that we observed on incubation of fresh lenses is possibly due to an increase in some acid ion, most likely an organic phosphate. The observed increase in total base of the lens supports such a view. However, the reversal of the cold-induced cation shift that occurs when the temperature is

raised to 37°C. cannot be attributed to such a mechanism since the potassium gained is roughly equivalent to the sodium lost.

DR. LUDWIG VON SALLMANN (New York): May I ask Dr. Harris whether he determined the cation shift in the early stages of experimental cataract? In preliminary experiments in which flame photometry was used for determinations of sodium content, we were unable to establish any increase of this cation in lenses irradiated with a relatively high dose one week prior to the determination.

DR. HARRIS: We have underway now such series of experiments, Dr. von Sallmann, using the lens of the alloxanized rabbit as our test lens. So far, we have carried our animals only to five weeks' post-injection. All I can say is that our experiments are hopeful. They indicate that a cation shift occurs and that it is reversible in vitro but it would be

hazardous to draw any definite conclusions at the present time.

Concerning radiation changes, I would anticipate, as I imagine you do, that after a sufficient period, postirradiation, the cation shift would be observed. Your studies with radioactive sodium and potassium indicate that such was certainly the case.

DR. DAVID SHOCH (Chicago): We have been doing some work at Northwestern University along the lines mentioned by Dr. von Sallmann, determining sodium, potassium, chloride, and total water in the lens following irradiation, and I would like to add that we, too, have found absolutely no changes in sodium or potassium before the advent of very obviously clinically perceptible cataracts.

As a matter of fact, the only gross changes in potassium and sodium occurred with what might be called mature cataracts. However, there were some very early changes in chlorides, in so-called chloride space, and in the water of the lens, which made us think that the first change was an uptake of water, perhaps intracellularly, by the fibers themselves.

I do not mean to imply at all that alteration in chloride concentration is responsible for the formation of cataract. I am sure that anions and cations, per se, have nothing to do with this. They are simply the reflection of a breakdown in metabolic processes.

DR. HARRIS: That is very interesting. We have not determined the chloride content of our lens but perhaps it would be a more sensitive index of what we are attempting to measure than is the change in the cation content.

We considered the question of the "chloride" and "sodium space" of the lens in the body of our paper but omitted it here for the sake of brevity. The "sodium space" which can be calculated from our

analyses is greater than the "chloride space" which Langham and Davson determined. This is not unexpected, of course.

Langham and Davson also calculated a "readily available space" from the distribution of radioactive sodium between the lens and aqueous in vitro. This value turned out to be considerably smaller than that which can be determined by direct analysis.

To me, this discrepancy reflects and emphasizes the fact that transfer equilibrium between the lens and extralenticular fluid may be slow to obtain. This is not surprising since the ratio of the surface area to the volume of the lens is small.

DR. DAVID G. COGAN (Boston): Dr. Harris, would it be a reasonable question to ask what the site is of this secretory activity?

Would it be a reasonable experiment to immerse a lens half-way into the fluid media; first the anterior surface immersed, and then the posterior surface immersed. In that way you might determine whether it is a vital activity of the epithelium that is responsible for it, or whether it is a property of the capsule by itself.

DR. HARRIS: That would be an extremely interesting experiment. We have not done it. We routinely rest the lens on its posterior surface because we feel that the changes are more likely to be occurring across the anterior surface.

We have thought all along that the barrier across which the active transfer occurs is a cellular membrane and that the capsule acts as a simple inert passageway. Before the meeting this morning, however, Dr. Dische told me that the data he will present today indicates that the capsule may not be an inert structure and that this active exchange of cations may also occur across the capsule.

CONTRIBUTIONS TO THE ENZYMOLOGY OF THE NORMAL AND CATARACTOUS LENS¹

III. ON THE CATALASE OF THE CRYSTALLINE LENS

E. A. ZELLER, M.D.*

Chicago, Illinois

In a number of biologic systems, the exclusion of oxygen reduces the effects of ionizing irradiation. In an attempt to interpret this phenomenon, some authors concluded that, in the presence of oxygen, hydrogen peroxide is formed by ionizing irradiation. The peroxide in turn acts on various chemical groups and thus disturbs the chemical organization of the cell.

If this conclusion were correct, the catalase (and peroxidase) activity of a given tissue must be of considerable importance to the mechanism of action of ionizing irradiation since, at low catalase concentration, the enzyme destroys certain peroxides, while at high concentration it functions as a peroxidase and thus helps to promote the irradiation effect.

Since, as it is well known, the lens is sensitive to irradiation, it seemed to be of interest, for the reasons already given, to study the catalase activity of the crystalline lens and thus to make some systematic contributions to the enzymology of the normal and cataractous lens.

There exists only one reference on lens catalase in the literature.² The experiments described there were carried out at a very early period, and, accordingly, a rather primitive method for determination was used. In addition, lens extract (from hog eyes) was not separated from the corpus vitreous. Nevertheless, the result indicated that there is little catalase activity in the lens. Actually, values are so low that, in order to obtain reliable results, a special method had to be developed, of which a description follows:

* From the Department of Biochemistry, Northwestern University Medical School. This study was supported in part by funds provided under contract AT (11-1) 118 between Northwestern University and the U.S. Atomic Energy Commission.

PREPARATION OF LENS HOMOGENATE

After removal of the lens from the eye, it is rolled on filter paper in order to remove traces of aqueous, vitreous, and iris. This procedure is repeated after rinsing of the lens with 0.9-percent sodium-chloride solution. The weighed material is transferred into a glass homogenizer containing saline. Homogenization takes place for three to five minutes in a bath of ice water, while care is taken to produce as little frothing as possible.

TITRIMETRIC PROCEDURES

The activity of lens catalase is so minute that the classical procedure³ which requires the titration of nondecomposed peroxide by 0.005 molar permanganate is by far not sensitive enough. Since the lens homogenates used are highly concentrated, the accuracy of the titration will also suffer from side reactions between permanganate and impurities.

In experiments in which purified catalase was added to lens homogenates, the iodometric determination⁴ turned out to be more satisfactory. In addition, the titrimetric procedures do not allow the use of optimal hydrogen concentrations which are in order of 0.5-molar solution⁵ but require approximately 0.01-molar peroxide.

MANOMETRIC PROCEDURES

It should be possible to measure catalase activity manometrically by following the liberated oxygen and thus avoid some of the disadvantages of the titrimetric procedures. Such attempts have been made repeatedly. However, it was shown that the values obtained by manometric methods are too low, between half and less than one tenth of those obtained by titrimetric methods.⁶

Since it was found that catalase is inactivated by adsorption on glass surfaces,⁷ it is very likely that the extremely small amounts of catalase usually present in the reaction mixture are in part adsorbed by the wall of the manometric vessel. By adding an inert protein such as gelatin⁸ to the solution, the glass wall is covered by this protein and the adsorptive inactivation of catalase may be prevented.

The same function should be performed by the high protein content of the lens homogenates. This is indeed true, as shown by experiments in which purified beef-liver catalase was added to lens homogenates (table 1). The combined catalase-lens homogenate solution is 2.3 times more active than the sum of activities of the individual components.

When hydrogen peroxide solutions are shaken in the Warburg apparatus, a spontaneous decomposition occurs which is of the same order, sometimes even higher, than the liberation of oxygen taking place in the presence of lens homogenate.

From such experiences, it was concluded that either the glass wall of the reaction vessel or traces of heavy metals accelerate the nonenzymic decomposition of hydrogen peroxide and that the proteins of lens homogenate prevent this action, for example, by binding heavy metal ions. It has to be mentioned here that glass-distilled water was used throughout all these studies.

TABLE 1

INFLUENCE OF LENS HOMOGENATE ON MEASUREMENT OF PURIFIED CATALASE

Lens Homogenate	Catalase (μ g)	Micromoles O ₂ after Six Minutes
—	0.66	0.8
0.2	0.66	2.2
1.0	—	0.7

Cattle lens, stored four weeks in deep freeze, homogenized with five volumes of 0.9 per cent saline. Purified beef-liver catalase, obtained from Armour. Phosphate buffer: pH 6.8, $\frac{M}{45}$ (final). H₂O₂-concentration: 0.5 M. Volume: 1.5 ml. Temperature: 19.6°C. Enzyme blanks subtracted.

TABLE 2
NONENZYMIC DECOMPOSITION OF
HYDROGEN PEROXIDE

Preparation	Oxygen Production (micromoles)
—	1.0
Lens homogenate	2.0
Heated homogenate	0.3

Homogenate prepared from freshly removed rabbit lenses. Part of homogenate heated for 15 minutes in a water bath of 60°C.

Measurement of oxygen production after 30 minutes of incubation. For other experimental conditions see Table 1.

In order to prove this assumption, non-catalase proteins such as egg albumin and heat inactivated lens homogenate (table 2) were added to the hydrogen-peroxide solution under the conditions of catalase determination.

As indicated by the results of Table 2, the presence of lens proteins, obtained by gentle heating, reduces the spontaneous decomposition of hydrogen peroxide to a third. A 2.6-percent solution of recrystallized egg albumin* reduced, under similar conditions, the oxygen output from 2.1 to 0.8 micromoles. For the calculation of the results, the values obtained from experiments such as described in Table 2 were used.

Other reaction conditions regarding temperature and buffer solutions were taken over from the literature (see list of references). The conditions, as described in Table 1, furnish reproducible values. Before the adoption of this procedure, some experiments were carried out at a temperature of 38°C. with a substrate concentration of 0.01 molar.

The Q-values (micromoles of oxygen per hour and per gram wet tissue) range from 30 to 110 for rabbit and cattle lenses (standard procedure) and from 16 to 30 for dog lenses (38°C.). Some of the variations are probably due to the fact that not only fresh lenses but also material stored in a deep-freeze for several weeks were used.

* I am indebted to Dr. H. B. Bull for a sample of recrystallized egg albumin.

These values are lower than those reported for all other tissues, with the possible exception of leukocytes.⁹ Thus, it seemed to be possible that the small catalase activity may be due to a contamination coming from surrounding tissues. But the determination of catalase activity of the aqueous and vitreous revealed values of the same order as found in the lens. In cattle vitreous, *Q* values of 19 and 39 (at 38°C.) were obtained. Results on aqueous will be presented in another paper.

In order to get some information about the distribution of the enzyme, the cattle lens was dissected by frontal cuts into three sections of approximately equal size. So far as our method permits us to make any conclusion, there is no difference in activity in the different sections of the lens.

CHARACTERIZATION OF LENS CATALASE

Since so many agents are able to catalyze the decomposition of hydrogen peroxide, it

was considered to be necessary to check if the reaction already described actually is caused by catalase.

As the results listed in Table 3 indicate, the agent is destroyed in part at 55°C. and completely at 60°C. The homogenates can be dialyzed overnight without loss of activity. In a quick-dialyzer¹⁰ which removes quantitatively 0.9-percent sodium chloride from the dialysis casing within three hours, the activity dropped in three hours to half of the activity (rabbit lens, measured at 19.6°C.).

Hydroxylamine strongly inhibits catalase. In rabbit lens homogenate, the degradation of peroxide (at 38°C.) was completely inhibited by 10^{-4} molar hydroxylamine solution, while 10^{-5} molar produced an inhibition of 70 percent. In dog lens homogenates 10^{-5} molar sodium azide, another inhibitor of catalase completely blocked the evolution of oxygen (38°C.).

CONCLUSIONS

In the lens of three species, a definite but very small amount of hydrogen peroxide decomposing capacity was found. The agent responsible for this reaction is heat-labile, does not dialyze through membranes and is blocked by typical catalase inhibitors. Thus, if hydrogen peroxide were produced in the lens in the course of ionizing irradiation, little protection to this organ can be given by its catalase.

TABLE 3
HEAT LABILITY OF LENS CATALASE

Temperature	<i>Q</i>	Inhibition (percent)
No heating	32	—
50°C.	30	6
55°C.	18	44
60°C.	0	100

Cattle lens homogenate heated in water bath for 15 minutes at temperatures given in above table. Same conditions as described in Table 1.

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THE CONTENT IN GLUTATHIONE AND NUCLEOTIDES OF THE LENS CAPSULE AND ITS RELATION TO LENS PERMEABILITY*

ZACHARIAS DISCHE, M.D., G. EHRLICH, Ph.D., C. MUNOZ, A.B., AND
L. VON SALLMANN, M.D.

New York

Changes in the permeability of the lens are considered by some authors^{1,2} to be a causative factor in certain types of cataract, such as galactose diabetes and radiation cataract. These changes could affect the lens capsule, the lens epithelium, or the fibers of the lens.

The lens capsule is generally considered to be an inert membrane chemically related to the intercellular substance of the connective tissue.

It seems, therefore, reasonable to expect that it will be metabolically inactive or less active than the cellular elements of the lens. It can be also assumed that it will differ in its composition, as far as certain intracellular constituents are concerned from the other elements of the lens in the same way as the intercellular substance of the connective tissue differs from its cellular constituents.

These differences in the composition between the cells and their surroundings are either due to the impermeability of the surface membranes for the respective constituents or due to a one-sided permanent active transport of those constituents driven by metabolic processes. The latter seems to be the case, according to Harris,³ as far as electrolytes are concerned.

Other constituents of the living cells which are in general absent in the intercellular fluid like mono- and polynucleotides and glutathione are probably unable to permeate the surface membrane of the normal cell. Any injury, however, to the cellular elements can

increase the permeability of this membrane for these substances and thus lead to their leakage into the cellular environment.

On the basis of these considerations, it could be expected that the inert capsule of the lens would be lacking in glutathione as well as in such mono- and polynucleotides as adenosinetriphosphate (ATP) and the coenzymes I and II, substances which play a predominant role in the cellular metabolism.

Changes in the permeability of the epithelium and of lens fibers would cause a leakage of these substances into the lenticular capsule. The content of the latter in these substances, therefore, could serve as an indication of increased permeability of the surface of the lens due to injury.

If such injury plays a role in the pathogenesis of certain forms of cataract, it should be possible to detect it by comparing the content of the lens capsule in glutathione and nucleotides under normal conditions with those prevailing in the early stages of the cataractous process.

To test this possibility we determined glutathione and the total nucleotides in the stripped-off lens capsule of beef and rabbit, under conditions approaching, as far as possible, normality, as well as under conditions which could be expected to increase the permeability of the cellular elements of the lens.

EXPERIMENTAL

MATERIAL

The beef eyes were obtained from the slaughter house. The eyes were supposed to be removed a short time after the death of the animal and to remain for about one to three hours in rooms cooled down to a few centigrades. They were brought to the labo-

*From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital. This work was performed under Contract #AT-30-1-Gen. 70 of the Atomic Energy Commission.

ratory packed in ice and the lenses were removed not longer than one-half to one hour after their arrival in the laboratory. The rabbit eyes were enucleated immediately after the death of the animal and used immediately for the experiment.

PREPARATION OF THE CAPSULES

Beef eyes were opened by excision of the cornea, one radial incision was made on the iris and ciliary body, which were then ripped out in toto. The zonular fibers presented themselves thus clearly and could be severed all around with sharp scissors without injury to the capsule.

The lens was then rotated so that the adherent parts of the vitreous could be removed. In the usual procedure, a cross section was carried out through the posterior cortex and the capsule, and the lens was then placed with the anterior surface down on a slide.

The lens capsule with the adherent posterior cortical layers was spread to allow the removal of the nucleus from the surface strata. The separation of the cortex from the lens capsule and epithelium could be achieved easily by lifting up the fibrous material at the proper plane.

Preparations were also made by equatorial incision of the lens capsule. In this case the anterior half of the lens capsule was prepared similar to the previously described technique; whereas, the posterior lens capsule could be drawn off the cortex in one piece by means of a fine forceps.

The removal of the lens epithelium from the lens capsule was carried out by scraping with a scalpel-like instrument under observation with the biomicroscope or under loupe magnification in the reflected light of a focused beam, which gave assurance that no epithelium had remained on the capsule.

In a few instances, the capsule preparations were embedded for histologic examination to confirm the absence of epithelial cells. In several series the anterior lens capsule was divided by fine scissors into the equator-

ial part and the central portion, which were then treated separately.

ANALYTICAL METHODS

For the determination of the nucleotides and glutathione, the lens capsules were deproteinized by the addition of enough trichloroacetic acid to make its final concentration five percent. The material was left for two hours in the icebox, to assure complete extraction, and centrifuged. The supernatant was used for the determination.

For the determinations in beef lenses, five to 10 capsules, in the case of rabbits, four to five capsules, were used for every set of determinations. Reduced glutathione was determined by the color reaction with glucose and tryptophane in H_2SO_4 , described previously.⁴ Nucleotides were determined by the orcinol reaction, using the technique described in 1937 by Dische and Schwarz.^{2a}

The density of the green solution in this reaction was measured at 665 millimicrons with Beckman spectrophotometer, at which wave lengths pentoses show the maximum absorption.

The lens capsule was found, however, to contain a considerable amount of glucose which in the orcinol reaction gives a yellow color instead of the green color of pentose. When the concentration of glucose exceeds a certain limit, the yellow reaction products give a sufficient strong absorption at 665 to cause a significant error in the determination of nucleotides. This error was eliminated in the following way:

With every set of the lens capsule extract, a standard of muscle adenylic acid (MAP) and of glucose was run. The absorption at 665 $m\mu$ of the known was compared with that of the muscle adenylic acid and glucose standard. Afterward a wave length around 580 $m\mu$ was found at which the density of the glucose standard was identical with that at 665 $m\mu$. This procedure was necessary because the absorption maximum for glucose in this reaction is not as constant as that for nucleotides.

The difference in the density of the unknown at 665 and 580, designated $D_{665}-D_{580}$, which is zero for glucose, is a measure for the muscle adenylic acid of the nucleotide in the unknown as well as in the muscle adenylic acid standard. The quotient $D_{665}-D_{580}$ of the unknown divided by $D_{665}-D_{580}$ for the standard gives the concentration of nucleotides in the unknown expressed in terms of muscle adenylic acid.

The nucleotide fraction of living tissue consists mainly of adenosinetriphosphate, of coenzymes I and II, and coenzyme A. When, in carrying out the orcinol reaction, the reaction mixture is heated 20 minutes at 100°C., the extinction coefficient of adenosinetriphosphate and the three coenzymes is practically identical. The total value for nucleotides obtained in this way represents the total concentration of muscle adenylic acid in the tissue present in form of free muscle adenylic acid, adenosinetriphosphate, or in form of coenzymes.

When the heating period, however, is only three minutes instead of 20 minutes, the muscle adenylic acid, present in form of the oxidized form of coenzymes I and II, reacts only half as strong as muscle adenylic acid in the form of adenosinetriphosphate.

By determining therefore, the total nucleotides expressed in terms of muscle adenylic acid after three minutes and 20 minutes of heating the reaction mixture, we are able to determine whether the unknown contains the two coenzymes, I and II, and as the concentration of coenzyme A is much smaller than that of coenzymes I and II, we can also estimate in this way the total amount of oxidized coenzymes I and II in the nucleotide fraction.

RESULTS

1. *The content in glutathione and nucleotides in lens capsules covered by epithelium.*

In the first series of experiments, glutathione and total nucleotides were determined in the anterior and posterior lens capsules separated from the lens. The anterior capsule

under these circumstances is covered by the epithelium. The results of these determinations are presented in Table 1.

As can be seen, the values for glutathione in the anterior lens capsule in eight determinations carried out on groups of five to 10 lenses ranged between 55.4 and 78.1 mg. percent in beef, and between 152 and 223 in three groups of five rabbit lenses, and the values for the total nucleotides expressed as muscle adenylic acid, between 34 and 83 mg. percent in beef lenses, and 103 and 120 mg. percent in rabbit lenses respectively (table 2). In the percent of nitrogen the values for glutathione varied between 3.8 and 5.9 percent, for nucleotides between 3.2 and 5.6 in beef capsules. In posterior beef capsules, in four determinations, 62.7 to 76 mg. percent glutathione and 53.3 to 134 mg. percent nucleotides were found per 100 gm. of wet weight.

2. *Glutathione and nucleotides in capsules deprived of epithelium.*

The weight of the epithelium as calculated from histologic data can be assumed as 2.0 mg. for a beef lens and 0.5 for a rabbit lens. These represent only about one twentieth of the weight of the anterior lens capsule. It seemed, therefore, from the beginning, improbable that the amount of glutathione and nucleotides found in the capsules would be derived exclusively from the epithelium.

To exclude this possibility, however, we carried out a series of determinations of these substances on beef lens capsules from which the epithelium was scraped off, as described previously. Two sets of these experiments were carried out.

In the first series, the determinations were performed on the whole anterior capsule deprived of the epithelium; in the second series, the anterior capsule was divided in a central part and in an equatorial part, the first representing about one third of the total weight of the capsule. This was done because the scraping off of the epithelium appeared to be much more complete on the central part of the lens than the peripheral part.

Glutathione and nucleotides were then de-

TABLE 1

CONTENT IN GLUTATHIONE AND NUCLEOTIDES OF BOVINE LENS CAPSULE AND ITS PARTS:
NUCLEOTIDES EXPRESSED IN TERMS OF ADENOSINE-5-PHOSPHATE

Experiment No.	Preparation	Number of Lenses	Wet Weight (in mg.)	Glutathione		Nucleotides		Nitrogen in Percent Wet Weight
				A	B	A	B	
169	Anterior capsule plus epithelium Posterior capsule	10	395.4			49.0	3.22	1.52
			145.4			53.3	4.9	1.07
176	Anterior capsule plus epithelium	5	265	73.2	5.9	37.5	3.12	1.28
142	Anterior capsule minus epithelium	10	330	59.4		47		
164	Anterior capsule minus epithelium a) Equatorial part b) Central part Epithelium				7.4		7.24	
					3.8*		4.7*	
					4.6		5.5	
					2.8		3.7	
170	Anterior capsule plus epithelium a) Equatorial part b) Central part Posterior capsule	10	359.6*	70.3*	4.9*	68.4*	4.9*	161*
			258	73.5	5.4	71	5.3	136
			101.6	54	2.7	61	3.6	2.00
			98	76	7	76	6.6	1.14
171	Anterior capsule plus epithelium a) Equatorial part b) Central part Posterior capsule	8	278.2*	61.8*	4.5*	83*	5.6*	1.56*
			206.3	66.4	5.2	85	6.2	1.28
			71.9	48	2.3	77	3.8	2.08
			75.3	68	5.4	134	7.7	1.18
179	Anterior capsule plus epithelium	7	327.5	54.4	4.4	42.9	3.24	1.25
174	Anterior capsule plus epithelium	10	430.8	56.6	4.7	33.4	2.8	1.30
172	Anterior capsule plus epithelium a) Equatorial part b) Central part Posterior capsule	9	329.1*	77.7*	4.9*			
			230	76.7	5.6			
			299.1	80.0	3.5			
			105.5	62.7	5.5			
158	Anterior capsule plus epithelium a) Equatorial part b) Central part	10	421*	78.1*	5.2*			152*
			273	83.6	6.5			129
				66.2	3.4			192

* Calculated as sum of the values for the equatorial and central parts.

A = Values in mg. per 100 gm. wet weight.

B = Values in mg. per 100 mg. N.

terminated in the two separated parts of the capsule. The scraped-off epithelium was also deproteinized by trichloroacetic acid and glutathione and nucleotides were determined in this extract. The results from two such experiments are presented in Table 1 (Ex-

periments 142 and 164).

While all the values for the lens capsule are calculated in mg. per 100 gm. wet weight, as well as in mg. per 100 mg. nitrogen, the values for the epithelium are only calculated in percent of nitrogen, as it was impossible

TABLE 2
GLUTATHIONE AND NUCLEOTIDE CONTENT IN RABBIT TOTAL LENS CAPSULES

Experiment No.	Number of Capsules	Wet Weight (in mg.)	Glutathione		Total Nucleotides		Nitrogen in Percent Wet Weight
			A	B	A	B	
167	5	51.2	223	14.5	120	7.8	1.54
166	5	58.7	198	15.4	103	8	1.29
138	5	49.2	152	10.7	119	8.3	1.42

A = Values in mg. per 100 gm. wet weight.

B = Values in mg. per 100 mg. N.

to weigh accurately the small amount of substance scraped off the surface of the capsule.

As can be seen from Table 1, the values for glutathione and nucleotides in the lens capsule after scraping off the epithelium do not essentially differ from those found in the intact capsule covered by epithelium.

The epithelium itself contains about 150 to 200 percent as much glutathione and nucleotides calculated on the basis of nitrogen as the lens capsule itself. If we assume that the protein content of the epithelium is about 20 percent of the wet weight, as is generally found in epithelium cells, then the concentration of glutathione and nucleotides by wet weight in the scraped-off epithelium seems to be essentially the same as that in the capsule itself.

3. Effect of storage of eyes on the content in glutathione and nucleotides of the lens capsule.

When the whole globe is kept for a few hours at room temperature or even at zero degrees, a considerable anaerobiosis of the lens must develop which can be assumed to cause injury to the epithelium and the superficial fibers of the lens. Under these conditions, therefore, an increase in permeability of these cellular elements can be expected.

The content in glutathione of the outermost part of the beef lens can be assumed to be about 250 mg. per 100 gm. wet weight. The content in nucleotides of the outermost part of the lens, the diameter of which corresponded to one fifth of the total diameter

of the lens, was found in this laboratory (Dische and Borenfreund) to vary between 100 and 120 mg. percent in terms of muscle adenylic acid.

The content in glutathione of the lens capsule of beef therefore corresponds to about one sixth to one third of that in the superficial parts of the lens and that of nucleotides to one third to two thirds. An increase in the permeability, therefore, of the surface layer of the lens and of the epithelium should manifest itself by an increase in the amount of these two substances in the capsule.

To test that, we first determined the variations in the concentration of these substances in two groups of 10 lens capsules each, which were stripped off simultaneously from eyes which all belonged to one single batch brought from the slaughter house. We found that, under these conditions, the deviation in the content in glutathione and nucleotides did not exceed 15 percent.

After that we determined these substances in lens capsules of beef which were left three to six hours either on ice or at room temperature, and compared them with the amounts of lens capsules stripped off from lenses of the same batch of eyes immediately after their arrival from the slaughter house.

As can be seen in Table 3, no marked increase in the content of nucleotides could be observed when the incubation at 4°C. did not exceed three hours. Glutathione, however, was already somewhat increased after this period of time. After incubation of six hours

TABLE 3
EFFECT OF STORAGE OF ENUCLEATED EYES ON THE CONTENT IN GLUTATHIONE AND NUCLEOTIDES OF THE LENS CAPSULE

Experiment No.	No. of Capsules	Preparation	Time and Temperature of Storage	Glutathione		Nucleotides	
				A	B	A	B
139	10	Anterior capsule minus epithelium	0 2 ^h 40' at 4°		6.1 7.0		3.6 3.8
142	10	Anterior capsule minus epithelium	0 2 ^h 40' at 4°		5.3 6.6		4.0 4.1
159	10	Anterior capsule minus epithelium a) Equatorial part b) Central part	0 6 ^h at R.T. + 16 ^h at 4° 0 6 ^h at R.T. + 16 ^h at 4°		5.8 10.4 4.1 8.1		3.8 4.7 1.9 2.4
158	10	Anterior capsule plus epithelium a) Equatorial part b) Central part	0 6 ^h at R.T. 0 6 ^h at R.T.	83.6 112 66.2 89.5	6.5 8.7 3.6 4.4	32.8 47.9 34.9 37.3	2.4 3.7 1.6 1.7
175	10	Anterior* capsule plus epithelium	0 3 ^h at R.T.			34.2 38.5	2.3 2.8
180	5	Anterior capsule plus epithelium	0 3 ^h at R.T.				3.5 3.4
181	5	Anterior capsule plus epithelium	0 6 ^h at R.T. + 16 ^h at 4°			87.5 101.4	

* Calculated from values for equator and central part.

A = Values in mg. per 100 gm. wet weight.

B = Values in mg. per 100 mg. N.

Nucleotides in term of adenosine-5-phosphate.

at room temperature, the content in nucleotides was also significantly increased.

These results suggest that the changes in the permeability of the surface layer of the lens develop slowly during the storage of the eyes and, only after at least six hours, are sufficiently great to permit a greater amount of nucleotides to pass into the capsule.

As glutathione has a lower molecular weight of about 300 against the molecular weight of the nucleotides, which varies between 500 and 700, the increase in the concentration of the first substance appears earlier than that of the second one.

4. *Effect of incubation in vitro of dry lens capsules on their content in glutathione and nucleotides.*

The absence of a significant change in the content in nucleotides of the lens capsule

after incubation in situ for no longer than three hours at 4°C. may be either due to the fact that the permeability during this period is not significantly affected, or to the fact that the glutathione, as well as nucleotides in the lens capsule, are permanently metabolized.

During this period, the decrease in amount due to this breakdown could be compensated by the slow leakage of these substances from the surface layers of the lens.

To test this possibility we incubated lens capsules containing the epithelial layer, as well as those deprived of it, for several hours either at room temperature or at 38°C. and determined the effect of this incubation on the amount of glutathione and nucleotides. Two series of experiments of this type were carried out.

In the first one, the lens capsules were transferred into air-tight vessels without any addition of fluid, kept for four to six hours at room temperature and then immediately deproteinized by the addition of trichloroacetic acid. The same number of capsules deproteinized immediately after the separation from the lens served for the determination of the initial values.

In a second series of experiments, five lens capsules were suspended in 1.0 cc. of a balanced salt solution recommended by Krebs,⁶ which has pH of 7.4, identical with the normal pH of the lens. Vessels containing the experimental samples were either left again for four to six hours at room temperature, or they were shaken in a water bath at room temperature in presence of pure oxygen to assure maximal supply of oxygen or nitrogen. The results of these experiments are presented in Table 4.

As can be seen from Table 4, in lens capsules incubated at room temperature for six hours without any addition of fluid, glutathione as well as nucleotides decrease to a very considerable extent, the first one by 65 to 80 percent, and the second one 30 to 60 percent. In samples which were suspended in the balanced salt solution and kept in an air atmosphere without any shaking, the decrease of glutathione was less pronounced especially in the equatorial part of the lens. The decrease of nucleotides, however, was not significantly affected (Experiment 174).

In Experiments 179 and 176 in which the samples were suspended in the salt solution, shaken in an oxygen atmosphere, the decrease in glutathione was as much as 90 percent. This shows clearly that the disappearance of glutathione is dependent upon the presence of oxygen in the atmosphere and consists in a catalyzed oxidation of this substance. The breakdown of nucleotides, on the other hand, seems to be independent of the oxygen and proceeds in an atmosphere of nitrogen.

DISCUSSION

Our observations demonstrate the presence of glutathione and various types of nucleotides in the stripped-off lens capsule of beef lenses, as well as rabbit lenses. The main bulk of these substances is present in the fibrous membrane itself and not in the epithelium, and the concentration by wet weight varies between 15 and 30 percent for glutathione and between one third to two thirds for nucleotides to that found in the superficial layers of the lens itself.

As these substances are not present in any significant amounts in the aqueous, the question arises whether they represent normal constituents of the lens capsule *intra vitam* or whether their presence in the capsule is due to a leakage which occurs immediately after death of the animal and would be due to a sudden decrease in the permeability either of the epithelium or the superficial lens fiber, or both.

The fact that these substances were found in capsules of rabbit lenses, removed a very short time after the death of the animal, and that their proportion to glutathione and nucleotides in the lens itself is about the same as in beef lenses, would seem to indicate that, if such a postmortem passage of these substances into the lens capsule occurs, it must occur within a few minutes after the death of the animal.

Our experiments on the effect of the storage of intact eyes at room or icebox temperature on the nucleotides and glutathione content of the beef lens capsule seem to exclude, however, the possibility that such a rapid passage could occur from lens fibers themselves. In this case, the difference in the concentration in the superficial lens fibers and the capsule should show a considerable further decrease after three hours' incubation.

These experiments, however, do not exclude the possibility that only the epithelium is involved in the sudden and very rapid passage which occurs after the death of the

TABLE 4
EFFECT OF INCUBATION IN VITRO OF LENS CAPSULES IN VARIOUS MEDIA ON THEIR
CONTENT IN GLUTATHIONE AND NUCLEOTIDES

Experiment No.	Preparation	Medium and Gas Phase	Time and Temperature of Incubation	Glutathione		Nucleotides	
				A	B	A	B
163	Anterior lens capsule minus epithelium a) Equatorial part b) Central part	None Air	0		7.5		6.1
			6 ^h R.T. + 16 ^h 4°		1.6		2.4
			0		3.2		3.6
			6 ^h R.T. + 16 ^h 4°		0.5		2.1
164	Anterior capsule minus epithelium a) Equatorial part b) Central part	None Air	0	68	4.6	80	5.5
			6 ^h R.T. + 16 ^h 4°	22	1.6	49	3.6
			0	59	2.8	78	3.7
			6 ^h R.T. + 16 ^h 4°	18	0.9	42	2.0
174	Anterior capsule plus epithelium a) Equatorial part b) Central part	Krebs* solution III Air	0	64	5.8	35	3.2
			6 ^h at 24°	35.2	2.9	17.6	1.4
			0	40.8	2.5	30	1.8
			6 ^h at 24°	10.8	0.6	13.7	0.8
179	Anterior capsule plus epithelium	Krebs* solution III O ₂ Atmosphere N ₂ Atmosphere	0	55.4	4.4	42.9	3.2
			6 ^h R.T.	4.8	0.38	19.3	1.5
			6 ^h R.T.	49.0	3.95	28.1	2.7
176	Anterior capsule plus epithelium	Krebs* solution III O ₂ Atmosphere	0	86	5.9	37.5	3.1
			3 ^h 38°	12.4	1.0	30.3	2.4
180	Anterior capsule plus epithelium	Krebs* solution III O ₂ Atmosphere O ₂ Atmosphere N ₂ Atmosphere	0			54.6	3.5
			2 ^h 38°			30.9	2.0
			4 ^h 29.5°			27.3	1.9
			4 ^h 29.5°			28.6	1.9
181	Anterior capsule plus epithelium	Krebs* solution III O ₂ Atmosphere N ₂ Atmosphere	0			87.5	
			6 ^h 23°			54.6	
			6 ^h 23°			60.4	

* ACTA Biochemica and Biophysica, 4: 250, 1950.

This balanced salt solution is prepared as follows:

83 parts of 0.9% NaCl

4 parts of 1.15% KCl

1 part of 2.11% KH₂PO₄

1 part of 3.82% MgSO₄ 7H₂O

3 parts of 1.3% NaHCO₃

18 parts of Na-Phosphate buffer (100 parts of 0.1 M, Na₂HPO₄)

(1.78% to Na₂HPO₄ · 2H₂O)

(1.38% NaH₂PO₄ · H₂O)

A = Values in mg. per 100 gm. of wet weight.

B = Values in mg. per 100 mg. N.

Nucleotides in terms of adenosine-phosphate.

animal. If this is the case, then we would have to assume that the concentration of glutathione and nucleotides in the epithelium intra vitam is very much higher than any ever found in any living cell.

A simple calculation shows that this assumption is not tenable. We find in rabbit

lens capsules a content in glutathione of up to 220 mg. percent by wet weight and of total nucleotides up to 120 mg. percent. Now the epithelium, on the basis of histologic evidence, can be assumed to represent about one twentieth of the volume of the capsule. If all the nucleotides and glutathione found

in the rabbit capsule were discharged from the epithelium after the killing of the animal, that would mean a concentration of about four percent of glutathione and 2.4 percent of total nucleotides in the epithelium.

Since most of the constituents of the nucleotide fraction are four basic acids, and glutathione can be regarded as one basic acid, such concentrations of the two components would make the epithelial cell highly hypertonic. It is clear, therefore, that the main bulk of these two substances in the lens capsule cannot be derived from the epithelium.

The data presented in Table 1 show that the concentration of nucleotides and glutathione vary from one group of lens capsules to another to a very considerable extent. As storage of lenses for several hours did not lead to any considerable increase of the concentration, as least of nucleotides, in lens capsules, these variations cannot be due to differences in the treatment of the enucleated eyes in the slaughter house, but must be due to other factors.

Two factors which were not rigidly controlled in our experiments and may be responsible for this phenomenon are the time of enucleation after the death of the animal and the age of the animal which allegedly varied between 18 and 30 months. It seems quite reasonable that every batch of eyes brought in from the slaughter house was obtained from a rather homogenous group of animals killed at a certain time in the slaughter house. Various batches brought at different times, however, may have originated from animals of different age.

On the basis of all these considerations, the assumption appears reasonable that the lens capsule permanently contains *intra vitam* nucleotides and glutathione as normal constituents, as do the epithelium and the lens fiber, although in somewhat lower concentrations.

The difference in the concentration of these substances in the lens capsule and the aqueous must be due to their inability to

permeate the outer surface separating the capsule from the aqueous. The presence of these substances, which are highly active in cellular metabolism in the capsule, strongly suggests that this membrane by no means is metabolically inert, as the intercellular substance of the connective tissue seems to be.

This assumption is further borne out by the fact that, as preliminary determinations established, the nucleotide fraction of the capsule has essentially the same composition as that of the lens fibers, which means that, apart from adenosinetriphosphate, that could be determined as phosphorus split-off by seven-minute hydrolysis in normal HCl, we find oxidized coenzymes I or II, or both, present in this fraction. The amount of this coenzyme fraction represents about one third to one half of the total nucleotides.

Further evidence of the metabolic activity in the lens capsule can be derived from the fact that the capsule is able to oxidize glutathione rapidly, and to break down the ribose which is a constituent of the nucleotides. Although the first reaction has not yet been proven to be an enzymatic one, the break down of the nucleotides requires the activity of specific enzymes.

Enzymes which are able to break down the ribose of nucleotides and nucleosides, first found in human red cells and later in all animal tissues,^{7,8} were recently shown to be represented by two different types of enzymatic systems.

One system is able to phosphorylate ribose in nucleotides with ribose-5-phosphate appearing as a final reaction product of the phosphorylated process. Ribose-5-phosphate, on the other hand, was shown to be broken down by a chain of enzyme reactions, the nature of which is not yet completely explored, and the breakdown products are resynthesized^{9a} to a mixture of hexose-monophosphate and hexose-diphosphate.

The metabolism of the nucleotides and nucleosides, therefore, finally enters into the metabolism of glucose. Ribose-5-phosphate has been shown to be a normal intermediate

in the oxidation of hexose-6-monophosphate by the so-called Zwischenferment. The enzyme system, which is able to convert ribose-5-phosphate to hexose-6-phosphate, therefore, appears to be complementary to the system which oxidizes hexose-6-phosphate; and the two systems together form a complete respiratory cycle. It seems possible that this type of respiratory process plays a major role in the metabolism of the lens capsule.

Recent experiments of Harris³ on the reversible exchange of electrolytes between the lens and the surrounding fluid indicate that the metabolic processes on the lens surface are a regulatory function and play a role in the regulation of the permeability of the lens surface. It appears very likely, on the basis of our observations, that the lens capsule itself is involved in these regulatory metabolic processes.

SUMMARY

1. The lens capsule *intra vitam* contains glutathione and various nucleotides. The amount of glutathione corresponds to 15 to 30 percent of that in the outer layers of the lens capsule, the amount of nucleotides 30 to 40 percent calculated per 100 gm. wet weight.

2. The content in these substances of the capsule is not changed significantly by a few hours' storage at low temperature.

3. The isolated lens capsule rapidly oxidizes glutathione during incubation at room or body temperature in presence of air, and breaks down ribose of the nucleotides anaerobically to yet unidentified end products.

4. After storage for at least six hours, at room temperature, the content of the lens capsule in glutathione and nucleotides is significantly increased.

630 West 168th Street (32).

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DISCUSSION

DR. V. EVERETT KINSEY (Detroit): We also have separated portions of the lens and determined the amount of adenosinetriphosphate. One of our results showed that the adenosinetriphosphate level in the posterior capsule of rabbit lenses, which contain no adherent epithelium, is higher than that in the adjacent posterior cortex, indicating that this compound may be concentrated in the capsule.

However, we find that the level in the anterior capsule with the adherent epithelium is about 0.5

mM/100 gm. of tissue much higher than that in the posterior capsule.

DR. DISCHE: We determined it also in the posterior capsule of beef eyes. It was as high as in the anterior capsule, and in certain cases it was even a little higher.

In these cases the weight of the nitrogen content of the posterior capsule was controlled and, if the nitrogen did not exceed more than 1.5 or 1.6 per-

cent, then we were sure we were not dealing with any significant number of lens fibers.

DR. DAVID G. COGAN (Boston): Dr. Kinsey, did you test the glutathione synthesis by lens capsule alone, or did you have any evidence to indicate whether the lens capsule synthesizes glutathione?

DR. KINSEY: No, we did not.

DR. JOHN E. HARRIS (Portland, Oregon): Dr. Dische's data and his interpretation present very intriguing possibilities. I think, too, that some of our previously published data support his view that the lens capsule acts as an active membrane, at least so far as the maintenance of the cation content is concerned.

When one nicks the lens capsule with a good-sized nick, regardless of whether it is the anterior or posterior surface, a rapid loss of potassium and gain of sodium occur. The exchange is not as extensive as one can produce under other conditions but is nonetheless appreciable.

This can readily be interpreted as indicating that an active transfer of cations occurs across the capsule, as well as across cellular barriers. Also, not infrequently in our experimental work with the excised lens, we have noted a pooling of water underneath a tense capsule, particularly when the cation content of the lens approaches that of the extralenticular medium. Obviously, this water must be held by some ion. The capsule, therefore, must

create a barrier to a certain degree.

I would agree that the capsule may be an active membrane and that the transfer of certain constituents across it may be metabolically mediated. In this respect then the lens can be likened to a giant cell, the membrane of which is the capsule. Perhaps, the effect of glutamic acid which we measured is in some way related to the glutathione of the capsule.

DR. E. A. ZELLER (Chicago): I would like to ask Dr. Dische if he has determined any enzyme activity in the capsule.

DR. DISCHE: No. We intend to make that extensive study, but so far we have been very much interested in the effect of the break down of the nucleotides because the recent experiments in various laboratories, as well as my own, indicate that the ribose 5-phosphate, which is the sugar in the nucleotides, is an intermediate in the general metabolism of practically all living cells, and it is related to the metabolism of glucose as well as to the other metabolic processes.

One part of this metabolism is anaerobic, and the ribose 5-phosphate can be anaerobically transformed into hexosephosphate. Therefore, we did not determine the metabolism of glucose, but I think this anaerobic break down of the ribose in the nucleotides indicates a very lively general metabolism of carbohydrates, because this is probably only one part of the metabolism.

STUDIES ON THE PHYSIOLOGY OF THE EYE USING TRACER SUBSTANCES*

PART IV. A COMPARISON OF THE STEADY-STATE RATIO OF SODIUM BETWEEN THE PLASMA AND AQUEOUS HUMOR IN NORMAL AND SCORBUTIC GUINEA PIGS

ROY O. SCHOLZ, M.D.
Baltimore, Maryland

Utilizing radiosodium (Na^{22}) as a tracer, I have reported^{1,2} a high concentration of sodium in the aqueous compared with the sodium in the plasma dialysate of the guinea pig. This pointed to the probability that sodium is secreted from the plasma into the aqueous of the species.

Friedenwald and his co-workers³ have

shown that ascorbic-acid deficient guinea pigs have a lowered rate of formation of intraocular fluid. The techniques used in my previous studies offer a convenient tool to study further the role of ascorbic acid in the secretion of the aqueous.

METHODS

Radioactive sodium (Na^{22}) was prepared by Dr. Dean Cowie in the 60-inch cyclotron of the Department of Terrestrial Magnetism, Carnegie Institution of Washington. The

* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital and the Carnegie Institution of Washington, Department of Embryology, Baltimore.

method of preparation and assay has been previously described.²

Guinea pigs of mixed sexes and weighing about 500 gm. were used. They were divided into two groups:

1. *The scorbutic group* which was fed a diet of roasted oats and water. This diet was supplemented with one drop of cod-liver oil three times a week. After about three weeks on such a diet, the pigs began to lose weight and showed hemorrhages in the buccal membranes.

2. *The control group* was fed the same diet and received in addition intraperitoneal injections of 10 mg. of ascorbic acid three times a week. This group did not show buccal hemorrhages and did not lose as much weight as the scorbutic group.

When a severe degree of clinical scurvy was manifest in the scorbutic guinea pigs, the animals were injected intraperitoneally with 0.75 cc. per kg. of a solution containing about 4.0 mM./cc. of radiosodium (Na^{22}) with a radioactivity of 4.0 mc. per cc.

After 24 hours, the animals were anesthetized briefly with ether and a sample of aqueous was removed with a small capillary pipette. The sample was adjusted to one of the calibration lines and then delivered to a small disc of filter paper which had been previously cemented* to the center of a copper disc. The sample spread evenly over the filter-paper disc.

To assure the same internal absorption of radioactivity in the plasma and aqueous samples, the same amount of nonradioactive plasma was added to the aqueous samples as was used for the plasma determinations.

Immediately after the sample of aqueous was removed, blood was taken by cardiac puncture. Samples of the serum were measured in the same pipette as the aqueous and were adjusted to the same calibration line as used for the corresponding sample of aqueous. These samples were also delivered onto filter-paper discs cemented on copper.

* Multilok diluted toluene.

An equal amount of water was added so that a similar amount of water and protein was present on both the aqueous and plasma discs. The samples were allowed to dry at room temperature. Measurements of the radioactivity of the samples were made with a Geiger-Müller tube and scaling circuit. The radioactivity of the samples was converted into micromoles of tagged sodium.

The amount of water in the guinea pigs' plasma was determined by drying weighed samples of plasma and subtracting the weight of the residue. The solids were found to be five percent of the total weight. The error involved in assuming the aqueous to be entirely water is less than 0.5 percent and consequently no correction was made for its salt content.

Additional 1.0 ml. samples of serum were used to determine the protein nitrogen. A modification of the direct nesslerization method of Koch-McMeekin was used. Total nitrogen was determined by diluting 0.1 ml. of serum with 9.9 ml. of normal saline.

One ml. of this dilution was treated with an acid digestion mixture and digested on an electric stove. The ammonia formed was nesslerized and the color compound was compared with a standard in a photoelectric colorimeter.

The nonprotein nitrogen was analyzed from a protein-free filtrate of serum. This was prepared using sodium tungstate and sulfuric acid. Two ml. of this filtrate was digested with an acid digestion mixture. The digested material was nesslerized and read in a photoelectric colorimeter.

The protein nitrogen, expressed as gm. per 100 ml. serum, was obtained by subtracting the nonprotein nitrogen from the total nitrogen.

RESULTS

The steady-state ratio of the sodium of plasma water to the sodium of the aqueous in scorbutic guinea pigs is 1.055 ± 0.01 (table 1).

The control guinea pigs, who were fed

TABLE 1
STEADY-STATE RATIO OF SODIUM OF WATER
OF PLASMA/SODIUM OF AQUEOUS
SCORBUTIC GUINEA PIGS

No.	Pe*/Ae†
1 R	1.007
L	0.992
2 R	1.098
L	1.110
3 R	1.043
4 R	1.089
L	1.026
5 R	1.007
L	1.058
6 R	1.066
L	1.071
7 R	1.051
L	1.079
8 R	1.108
L	1.037
9 R	1.034
L	1.027
10 R	1.038
L	1.039
11 R	1.093
L	1.072
Average = 1.055 ± 0.01	

* Pe = concentration in plasma water of Na (sodium tagged with Na²²) when aqueous is at equilibrium with the plasma.

† Ae = concentration in aqueous of Na when aqueous is at equilibrium with the plasma.

the same diet as the scorbutic and with an ascorbic acid supplement, had a steady-state ratio of the sodium of plasma water to the sodium of the aqueous of 0.985 ± 0.01 (table 2).

The microchemical studies on the plasma of these guinea pigs showed (table 3) a protein nitrogen of 0.71 ± 0.043 gm. percent in the scorbutic, 0.80 ± 0.045 in the scorbutic animals given an ascorbic-acid supplement, and 0.92 ± 0.031 in guinea pigs fed a laboratory diet of rabbit pellets and fresh greens with supplements of ascorbic acid.

DISCUSSION

There is evidence in the literature³ that ascorbic-acid depletion of guinea pigs profoundly affects the oxidation reduction potential of the ciliary tissues. The active transfer of acid and basic dyes in the ciliary tissue is reduced in the absence of ascorbic acid. Further, the rate of flow of the intra-ocular fluid is greatly reduced.

The steady-state ratio of sodium of plasma water to the sodium of the aqueous is compared in the normal, nonscorbutic controls, and scorbutic animals (table 4). It is seen that the normal guinea pigs have a ratio of 0.977 ± 0.0055 and the nonscorbutic controls have a ratio of 0.985 ± 0.01 , or essentially the same ratio, indicating that sodium is probably secreted from the plasma into the aqueous of this species if ascorbic acid is present in the diet.

The scorbutic animals, on the other hand, have a ratio of 1.055 ± 0.01 or approximately that of a dialysate as calculated for a Donnan equilibrium. This evidence suggests that ascorbic acid is essential for the secretion of sodium into the aqueous from the plasma.

The protein nitrogen chemical studies

TABLE 2
STEADY-STATE RATIO OF SODIUM OF WATER
OF PLASMA/SODIUM OF AQUEOUS
CONTROL GUINEA PIGS

No.	Pe*/Ae†
1	0.969
2	0.949
3 R	1.021
L	1.008
4 R	1.020
L	0.968
5 R	0.941
L	0.913
6 R	0.961
L	0.941
7 R	0.976
L	0.965
8 R	1.004
L	1.012
9 R	1.012
L	0.992
10 R	1.007
L	0.990
11 L	0.845
12 R	0.988
L	1.054
13 R	1.034
L	1.019
14 R	1.015
15 R	1.005
L	0.998
Average = 0.985 ± 0.01	

* Pe = concentration in plasma water of Na (sodium tagged with Na²²) when aqueous is at equilibrium with the plasma.

† Ae = concentration in aqueous of Na when aqueous is at equilibrium with the plasma.

TABLE 3

PROTEIN NITROGEN STUDIES ON SERUM OF
NORMAL NONSCORBUTIC CONTROLS AND
OF SCORBUTIC GUINEA PIGS

Experiment	Protein Nitrogen (gms./100 ml. serum)
Normal Diet	1.05
	0.85
	0.94
	0.87
	0.93
	0.87
	Average = 0.92 ± 0.031
Nonscorbutic Controls	0.68
	0.85
	0.80
	0.91
	0.83
	0.75
	Average = 0.80 ± 0.045
Scorbutic	0.67
	0.76
	0.51
	0.57
	0.73
	0.71
	0.89
	0.79
	Average = 0.71 ± 0.043

were undertaken to determine if there were any marked changes in the character of the serum of the scorbutic and control animals. A comparison of the values in Table 3 shows that, while there is slightly more protein nitrogen in the normal guinea pigs, 0.92 ± 0.031 gm. per 100 ml. serum, there is no significant difference between the non-scorbutic controls 0.80 ± 0.045 gm. per 100 ml. serum, and the scorbutic animals 0.71 ± 0.043 gm. per 100 ml.

SUMMARY

1. Radiosodium (Na^{22}) was used as a tracer to study the distribution of sodium

TABLE 4

STEADY-STATE RATIO OF SODIUM OF WATER
OF PLASMA/SODIUM OF AQUEOUS
GUINEA PIG

Experiment	Pe*/Ae†
Normal‡	0.977 ± 0.0055
Nonscorbutic Controls	0.985 ± 0.01
Scorbutic	1.055 ± 0.01

* Pe = concentration in plasma water of Na (sodium tagged with Na^{22}) when aqueous is at equilibrium with the plasma.

† Ae = concentration in aqueous of Na when aqueous is at equilibrium with the plasma.

‡ Previously reported.²

between the plasma and aqueous of the scorbutic and nonscorbutic guinea pig.

2. The steady-state ratio, sodium of plasma water to sodium of the aqueous was found to be $0.985 \pm$ in nonscorbutic control guinea pigs and $1.055 \pm$ in scorbutic guinea pigs.

3. No significant difference was found in the protein nitrogen of the serum of scorbutic (0.71 ± 0.043 gm. percent) or non-scorbutic controls (0.80 ± 0.045 gm. percent). There is slightly more protein nitrogen (0.92 ± 0.031 gm. percent) in the serum of guinea pigs on a normal laboratory diet.

4. In the absence of ascorbic acid the secretion of sodium into the aqueous of the guinea pig is diminished so that the ratio of sodium of plasma water to sodium of aqueous is 1.05 or approximately that of a dialysate as calculated for a Donnan equilibrium.

11 East Chase Street (2).

I gratefully acknowledge the material and assistance given me by Dr. Dean B. Cowie of the Carnegie Institution of Terrestrial Magnetism of Washington, D.C., and the technical assistance of Miss Celestia Weeks of the chemistry department of the Johns Hopkins Hospital.

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DISCUSSION

DR. DAVID G. COGAN (Boston): If I interpret it correctly, Dr. Scholz, your findings are consistent with the concept that vitamin C is essential for the secretion of sodium into the anterior chamber.

DR. SCHOLZ: That is right.

DR. V. EVERETT KINSEY (Detroit): I believe Dr. Bărâny pointed out about a year ago that the rate of flow of aqueous humor in normal and scorbutic guinea pigs was the same, and, since it seems probable that the secretion of sodium bears some relation to the flow of aqueous as a whole, I would like to ask Dr. Scholz if he has any suggestions as to how to bring these two sets of experiments into compatibility.

DR. SCHOLZ: I have none.

DR. JONAS S. FRIEDENWALD (Baltimore): May I pinch hit on this? Dr. Bărâny measured the rate of turnover of para-amino-hippuric acid in normal and scorbutic guinea pigs, and found no significant difference. Dr. Scholz has now found a significant difference in regard to the sodium concentration.

This raises the question as to whether there can be a systematic or theoretical error in either of these two contradictory results.

There is a possibility of a theoretical error in the para-amino-hippuric acid method of determination, which I have discussed with Dr. Kinsey, so he already knows this answer. It is this:

The method which Dr. Bărâny and Dr. Kinsey

worked out, for estimating rate of flow with the para-amino-hippuric acid as an indicator, consisted in injecting the test indicator intravenously. They chose this substance because it is rapidly eliminated from the blood by the kidneys, and they hoped to find a situation in which an appreciable concentration remained in the aqueous after the blood level had come down to almost zero, and then to measure the disappearance from the aqueous as an index of the rate of flow of water.

When any test substance enters the eye it distributes itself not merely in the anterior chamber but also in the posterior chamber, vitreous and lens. If now the blood level becomes zero, fluid coming into the posterior chamber would have no test substance, but it would collect some test substance from the vitreous and lens, and contribute that moiety to the anterior chamber. Consequently, what is being measured by the Bărâny-Kinsey technique with para-amino-hippuric acid is a partial estimate of the rate of flow of water and a partial estimate of the rate of clearance of the vitreous and lens. Which of those two factors predominates in the estimate is something that cannot be determined theoretically in advance.

If it is the latter that predominates, then there is no reason why that rate should change in the scorbutic animal, and consequently the paradox between Bărâny's work and Scholz's might be explained.

That is a possibility that has not yet been adequately documented, but is one way in which this disagreement might be resolved.

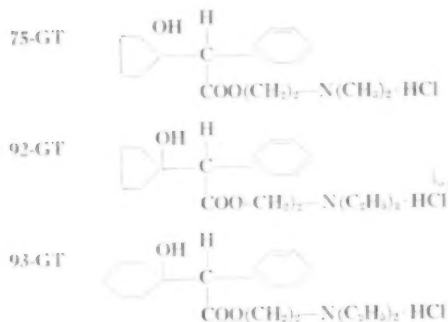
THE USE OF SEVERAL NEW DRUGS AS SUBSTITUTES FOR HOMATROPINE

SAMUEL V. ABRAHAM, M.D.
Los Angeles, California

INTRODUCTION

Some time ago, three drugs¹ were tested as to their mydriatic and cycloplegic powers in comparison with the present widely used drug, homatropine. A previous report on one of these drugs, Compound 75 GT, has been made by Priestley and Medine.² Several other men³ have studied this compound. These workers reported favorably on the mydriatic and cycloplegic effect of Compound 75 GT as compared to homatropine.

These compounds belong to a new series of spasmolytic agents belonging to the basic esters of substituted phenylacetic acids.⁴ These compounds have the following structural formulae:



This report gives the results of a comparative study of each of these drugs in 0.5-percent solution with a 2.0-percent solution of homatropine hydrobromide. In addition, this report includes a comparative study of Compound 75 GT with Compound 92 GT and Compound 93 GT, all 0.5-percent solutions.

In this clinical study, the subjects were all private patients. Most of these patients were brunettes with brown irises. Approximately 10 percent were blondes with blue irises. Ten of the patients were highly pigmented, either Negroes or Mexicans.

METHOD

In each subject, one eye received one of the drugs; the other eye, another drug. These drugs were instilled in the conjunctival sac in solution form, equal amounts of the solution being used in each eye. In some cases, only one instillation of each drug was used; in some, three instillations of each drug were made at 10-minute intervals; in still others, six instillations of the drugs were made at 10-minute intervals.

The pupils were checked for size and reaction to light, in most of these cases, 10 to 15 minutes after the first or only instillation. They were again checked 30 to 40 minutes after this instillation. In cases in which patients received six instillations, the second examination was frequently omitted until 60 to 70 minutes after the first installation.

To check mydriasis, these patients were further examined for pupillary size 18 to 72 hours later, depending on the convenience of the patient.

In suitable patients, after objective refraction, the effect of the drug on the accommodation was studied. In some cases this study was made about 45 minutes after the instillation of the first or only drop; in cases with six instillations, this examination was made 75 minutes after the first instillation. Again the accommodation was studied, 18 to 72 hours later.

In studying the accommodation under cycloplegia, a plus lens was usually necessary to bring the type into focus. In most of the cases in which this was studied, the plus lens used in each eye was the same and the far point, as well as the near point of accommodation with this additive lens, was determined. The far point was approximately the same in each eye of each individual, indicating the dependability of the

objective refraction. The variation in the near point, then, was chiefly due to changes in accommodation.

In Groups I-A, I-B, and I-C, homatropine hydrobromide was used in one eye. In the other eye, Compound 75 GT (Group I-A), Compound 92 GT (Group I-B), and Compound 93 GT (Group I-C) were used as indicated. Compound 75 GT was used in one eye in Group II-A while in the other eye, Compound 92 GT was used. In Group II-B Compound 75 GT was used in one eye and Compound 93 GT was used in the other.

OBSERVATIONS

MYDRIASIS

In all cases, the pupils were measured at the onset and found equal in size and equally active. The average pupil size as examined under 20 candle power was 3.0 mm., varying in size between 2.0 mm. and 4.0 mm.

Table 1 presents the data concerning the mydriatic effect of the three compounds (75, 92, and 93) as compared with that of homatropine hydrobromide. Observations were made at varying intervals during a 70-minute period after beginning of the experiments. In none of the observations were there any reversals; that is, in no case was a pupil larger than its mate at one observation and smaller later during the 70-minute period. From this table, it may be seen that Compounds 75, 92, and 93 GT all affected the size of the pupils to a greater extent than did homatropine.

The degree of mydriasis was similar for

TABLE 1

MYDRIATIC EFFECT OF COMPOUNDS 75, 92, AND 93 GT COMPARED WITH HOMATROPINE (10 to 70 minutes after initial or only instillation)

Drug Used	Cases with Pupils >H		H	=H	Total No. Cases
	#	%			
75	79	67.0	12	27	118
92	45	67.2	5	17	67
93	48	66.6	5	19	72

the three drugs, whether one, three, or six instillations were used. Each showed a greater effect on mydriasis with each additional instillation. The average pupil size is shown in Table 2.

The reaction to light, for the most part, was related to the pupil size—the smaller the pupil, the greater the reaction to light. When a difference in pupil size existed, the reaction to light was less or nil in the larger pupil when examined 30 to 40 minutes after initial instillation.

In every case in which the pupil was larger in 30 to 40 minutes, or even in 60 to 70 minutes, the larger pupil had shown dilation earlier than the other pupil. Therefore, whatever is noted concerning degree of mydriasis applies to speed of mydriasis.

Speed of recovery could not be accurately determined. However, the pupils were checked on the patients' return visits (18 to 72 hours after the instillation whenever possible). Frequently the pupils were equal. When a difference did exist, the "homatropine eye" showed the larger pupil in at least 28 of the eyes in which Compound 75 GT had been used in the other eye. In 18 of these eyes the "75 eye" had previously shown the greater mydriasis. This can only mean that the pupil receiving Compound 75

TABLE 2

EFFECT OF NUMBER OF INSTILLATIONS ON PUPIL SIZE AT APPROXIMATELY 30-MINUTE (1 AND 3) AND 60-MINUTE INTERVALS (6)

Drug	No. of Instillations		
	1	3	6
Homatropine	5.65	6.5	8.08
GT 75	6.5	7.42	8.38
GT 92	6.8	7.5	8.38
GT 93	6.1	7.3	8.30
No. Cases	181	36	40
Ages (years)	7-93	30-40	4.5-19

TABLE 3
MYDRIATIC EFFECT OF COMPOUNDS 92 GT AND 93 GT COMPARED WITH COMPOUND 75 GT
(10 to 70 minutes after initial or only instillation)

Drugs Used	Cases with Pupils					Total No. Cases
	>75		<75		=75	
	#	%	#	%		
92	14	21.9	10	15.6	40	64
93	5	13.0	18	46.0	16	39

GT recovered more quickly from the mydriatic effect of the drug.

This was not so for Compounds 92 GT and 93 GT. In these cases, whenever a difference in pupils was observed, the more dilated pupil was the one receiving these drugs, even though the "homatropine pupil" had previously been larger in two cases. In other words, Compounds 92 GT and 93 GT produce a longer-lasting mydriasis than homatropine.

Table 3 shows the results of a comparative study of Compound 75 GT with Compounds 92 GT and 93 GT. Here it is indicated that Compound 92 GT is slightly more effective, while Compound 93 GT is definitely less effective, as a mydriatic than is Compound 75 GT. However, the recovery time is definitely more rapid with Compound 75 GT. Compounds 92 and 93 GT affected the pupil size for as long as a week in some cases. The pupils, when checked 18 to 72 hours after instillation, usually showed a consistent difference in size, the smaller and more active pupil belonging to the "75 eye."

CYCLOPLEGIA

The observations on accommodation were made immediately after objective refraction was done at the time of dilatation and again 18 to 72 hours later.

In 17 cases, the eye receiving the homatropine showed a deeper cycloplegia 45 minutes after the initial or only instillation when compared with Compound 75 GT. In 19 cases the cycloplegia was greater in the "75 eye." In 34 cases, no definite difference could

be demonstrated.

When these cases were tested 18 to 72 hours later, the "homatropine eye" showed the weaker accommodation in 22 cases. There were no cases in which the "75 eye" showed a greater amount of cycloplegia than the "homatropine eye."

Compounds 92 GT and 93 GT showed a definite tendency to produce a longer-lasting cycloplegia. The accommodation was deficient in most cases tested on the post-cycloplegic visit, even though there had been no difference when tested 45 to 75 minutes after instillation. At least four cases showed that the "92 eye" was still deficient in accommodation four days after instillation. On direct comparison with Compound 75 GT both Compounds 92 and 93 produced longer-lasting cycloplegia in most cases tested.

EXAMPLES

Case 1. A girl, aged nine years, received one drop of homatropine in the right eye and one drop of Compound 75 GT in the left eye.

The far point of accommodation of each eye with a +2.5D. sph. added to objective refraction was: R.E. and L.E., 14 inches. The near point was: R.E., 9.0 inches; L.E., 11 inches. Residual accommodation was 0.808 diopters less in the "75 eye" 45 minutes after instillation. Approximate residual accommodation was: R.E., 1.5 diopters; L.E., 0.72 diopters.

Case 2. A boy, aged 12 years, received one drop of homatropine in the right eye. Compound 75 GT was instilled in the left eye.

With a +2.5D. sph. added to objective refraction, the far point of accommodation in the right eye was 40 cm.; in the left eye, 39 cm. The near point was: R.E., 22 cm.; L.E., 27 cm. Residual accommodation was: R.E., 2.0 diopters; L.E., 1.2 diopters. Compound 75 GT produced a deeper cycloplegia by 0.8 diopters.

When rechecked 48 hours later, the near points were: R.E., 30 cm.; L.E., 22.6 cm. These readings were made with no addition to the correction for error of refraction. Recovery is obviously faster for Compound 75 GT.

Case 3. A man, aged 44 years, received one drop of homatropine in the right eye and one drop of Compound 75 GT in the left eye. Refraction showed: R.E. and L.E., +0.25D. sph. under cycloplegia. Pupils were equal (7.0 mm., each).

With a +2.5D. sph. added, the near point of accommodation was: R.E., 33 cm.; L.E., 26 cm. Residual accommodation was: R.E., 0.5 diopters; L.E., 1.25 diopters, showing a difference of 0.75 diopters.

Examination 24 hours later showed the pupils to be equal. Vision was: R.E., 1.0; L.E., 1.0 (plano). The near point of accommodation with a +1.5D. sph. added was 24 cm., O.U.

Case 4. A young woman, aged 20 years, received one drop of homatropine in the right eye and one drop of Compound 75 GT in the left eye.

In 45 minutes the pupils were: R.E., 7.0 mm.; L.E., 7.5 mm., and were fixed to light. Refraction showed: R.E., +6.25D. sph. \ominus +0.25D. cyl. ax. 90°; L.E., +6.75D. sph. \ominus +0.25D. cyl. ax. 90°. This patient had never worn glasses and had uncorrected vision of 1.0 in each eye.

The near point of accommodation was: R.E. (without add to cycloplegic findings), 10 inches; L.E. (with a +1.5D. sph. add), 10.25 inches.

On re-examination 48 hours later, the manifest refraction showed: R.E., +3.5D. sph. \ominus +0.25D. cyl. ax. 90°; L.E., +4.0D. sph. \ominus +0.25D. cyl. ax. 90°. Each eye easily accepted +3.0D. less than the cycloplegic findings. The near point then was: R.E., 15 cm.; L.E., 12 cm.

SENSITIVITY

Not many patients shows a sensitivity to homatropine, only one was encountered in this series. This patient's other eye with Compound 75 GT remained pale. The slight congestion frequently noted with homatropine was never noted in the eyes receiving Compounds 75 GT, 92 GT, or 93 GT. Occasional complaints of smarting for a few moments were noted for all drugs used.

TENSION

In one case, the eye receiving Compound 75 GT showed a tension reading of 33 mm. Hg (Schiotz) 40 minutes after initial instillation of the drops. The tension in the other

(homatropine) eye was 22 mm. Hg (Schiotz). The diameter of the pupil showing the higher tension was 7.5 mm.; the other, 6.5 mm. The tension was easily controlled with pilocarpine.

In another case in which glaucoma was suspected by another doctor, the eye receiving Compound 75 GT showed a tension of 29 mm. Hg (Schiotz); the other eye showed a tension of 22 mm. Hg. No miotic was used and two days later the tension in each eye was 22 mm. Hg. In both cases visual fields and vision were normal.

Tension studies were made on 40 patients over 40 years of age. There were no appreciable differences in tension in the two eyes of each case and no pathologic tensions except as have just been noted.

CONCLUSIONS

In this clinical comparison of three new drugs with homatropine hydrobromide, it was found that all three drugs compared favorably with homatropine. These drugs in 0.5-percent solution tended to produce mydriasis more rapidly and to a greater degree than did a 2.0-percent solution of homatropine hydrobromide.

Compound 75 GT^s tended to produce a deeper cycloplegia, which was usually of shorter duration, than that produced by homatropine. Compounds 92 GT and 93 GT produced longer-lasting cycloplegia. Compound 75 GT produces no signs of local irritation and only occasional mild smarting.

As a factor in the production of acute mydriatic glaucoma, the data presented are insufficient for definite conclusions. One may state, however, that the tendency to produce a greater mydriasis may favor production of the glaucoma, while the definite decrease of signs of irritation may more than balance this. For Compound 75 GT, the shorter duration of the mydriasis may also tend to offset the potential danger of the larger pupil.

The new drug may be a valuable addition

to our armamentarium. It may easily replace homatropine. In a few cases in which this compound was compared with atropine, the

effect on accommodation has been surprisingly good. Further study is indicated.
6363 Wilshire Boulevard (48).

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3. Personal communication from Schieffelin and Company.
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5. Soon available under the trade name; Cyclogyl.

DISCUSSION

DR. JAMES E. LEBENSOHN (Chicago): Additional types of mydriatic and cycloplegic drugs are definitely needed, especially when dealing with atropine sensitivity. Unfortunately none of the newer synthetic drugs approach atropine in power and duration. Several are good substitutes for homatropine, but that is not the real need.

I have used each of the newer cycloplegic drugs in several hundred cases, starting with dibutoline (Merck) which was developed nearly 10 years ago. It is still not on the market, possibly because it is a surface-acting drug and causes a slight disturbance of the corneal epithelium, though personally I have not found that significant.

Several of the newer synthetic mydriatics should be commercially available since the patient may develop sensitivity to one of them. For example, a patient of mine was sensitive to atropine, homatropine, and hyoscine which are chemically interrelated. He used dibutoline for a year without any reaction. I then changed to BL-139, one percent (Bristol Laboratories), which produces a longer and stronger mydriatic action than the other synthetic drugs. It is the nearest approach to atropine and exerts about half the strength of the latter. After using this BL compound for 14 months, some sensitivity occurred, though very mild to that experienced with atropine. Dibutoline was again dispensed and to-date (over 14 months) no sensitivity reaction has resulted.

The cycloplegic drugs now under investigation include, besides the three discussed by Dr. Abraham and the two others just mentioned, two Blicke's compounds being investigated by Winthrop-Stearns and Merrell Company, respectively. As a substitute for homatropine, GT-75 is ideal as it acts more rapidly, the duration is shorter, and it is quite reliable. I have used it satisfactorily in several hundred cases. As a substitute for atropine, the best product offered so far has been BL-139, one-percent solution.

DR. IRVING H. LEOPOLD (Philadelphia): I think this is a very thorough study, in that there have been 300 or more cases which have been tested with these Schieffelin compounds. I believe it is

unfortunate that Dr. Abraham had to shorten his paper to fit the time limit for he apparently had to omit mentioning the methods by which he measured the cycloplegic effects of these drugs.

Dr. Gettes, at the Wills Hospital, has had some experience with these agents and found very much what Dr. Abraham reported here—that GT-75 is quite an effective agent and comparable in activity to two- and to four-percent homatropine. Others of this series were more potent than GT-75 and no more toxic.

Dr. Lebensohn is quite correct that we have need for new cycloplegic agents, ones which are of value not only for refraction purposes but also for relaxation of the ciliary body and iris musculature in cases of uveitis, where we encounter most of our upsetting sensitivity to atropine and scopolamine.

DR. DAVID G. COGAN (Boston): Will you tell us how you tested your animals, Dr. Abraham?

DR. ABRAHAM: In abbreviating the paper, I neglected to report the fact that I did cover the various other factors involved in comparing one drug with another, for instance, sensitivity.

I found that, while occasionally one finds eyes that are immediately sensitive to homatropine—and I found one such case in this series. More frequently one finds eyes that become particularly injected. However, I found no such case as this among any of the cases in the study. In one patient, one eye was particularly sensitive to homatropine; the other eye remained quite pale with the use of GT-75.

All the eyes in this study showed definite lack of sensitivity to any of these drugs. There were complaints of smarting, but the complaints were not particularly severe.

As far as the effect on tension is concerned, in one case, the eye receiving GT-75 showed a tension of 33 mm. Hg (Schiotz) 40 minutes after initial instillation of the drops. The tension in the other (homatropine) eye was 22 mm. Hg (Schiotz). The pupil showing the higher tension measured 7.5 mm.; the other 6.5 mm. The tension was easily controlled with pilocarpine.

In another case in which another doctor suspected glaucoma, the eye receiving compound GT-75 showed a tension of 29 mm. Hg (Schiotz); the other eye, 22 mm. Hg. No miotic was used, and two days later the tension in each eye was 22 mm. Hg. In both cases, visual fields and vision were normal.

Tension studies were made on 40 patients over 40 years of age. There were no appreciable differences in tension in the two eyes of each case, and no pathologic tensions except as noted.

As far as the question of cycloplegia is concerned, a couple of cases will illustrate the method of determining the residual accommodation. After all, either we have confidence in our objective refraction, or we do a subjective refraction at the same time.

I belong to the first group. However, I double-checked by using a plus lens while the patient was under cycloplegia, sufficiently strong—around 2.5 diopters—which brought the type into sharp focus about 13 or 14 inches from the eye. I tested the far point and the near point. If the far point was about the same, it was assumed that the objective refraction was probably equally accurate. Then I tested the near point, and the difference in the readings at the near point would tell me whether or not the cycloplegia was greater in one eye than in the other.

Here is a case in which homatropine was used in one eye and GT-75 in the other (the left) eye. Refraction happened to be plus 25 under cycloplegia. The pupils were equal, 7.0 mm. each, with a plus 2.5 add. The near point (right eye) was 33 cm., and in the left eye was 26 cm. In this case the residual accommodation in the right eye was 0.5 diopter and in the other eye 1.25 diopters. Upon examination 24 hours later the pupils were equal, the manifest refraction was plano, O.U. Vision was 20/20 in each eye. The near point of each eye was 24 cm.

Another patient, at the age of 20 years, had never worn glasses and the case was interesting from that point of view. The error of refraction under cycloplegia was: R.E., +6.25D. sph. \ominus 0.25D. cyl. ax. 90°; L.E., +6.75D. sph. \ominus +0.25D. cyl. ax. 90°. The near point without an add to the cycloplegic findings was 10 inches in the right eye and in the left eye with the plus 1.50 add required to begin the test, it was 10.25 inches.

The GT-75 compound had that much greater power on the ciliary body. Forty-eight hours later the cycloplegic test was done and the patient accepted three diopters less than the cycloplegic findings. The near point in the right eye was 15 cm. and the left eye was 12 cm. In other words, the recovery was more rapid in the left eye.

DR. LUDWIG VON SALLMANN (New York): In a small series of patients at Presbyterian Hospital in which we used the compounds under discussion, the findings of Dr. Abraham were, in general, confirmed. I was interested to hear that in two cases

Dr. Abraham also observed a rise of intraocular pressure after the use of GT-75. We had the misfortune to produce with this compound a glaucomatous attack in both eyes of a patient in whom no disposition to glaucoma was suspected. I should like to know whether Dr. Abraham feels that the rapidity of the dilatation of the pupil has anything to do with this unfavorable response.

DR. ABRAHAM: About 20 years ago I made a report on mydriatic glaucoma. The report was based primarily on a questionnaire. It indicated that acute glaucoma could occur at any time if the pupil was large enough and there was a vasomotor disturbance strong enough to cause an increase in the blood volume in the eye.

It had nothing particular to do with the speed of the attack; it just happened that the pupil was still too large and the circulation was still too disturbed at the time of the attack.

DR. DAVID G. COGAN (Boston): I would like to make a comment that does not apply to Dr. Abraham's remarks but rather to drugs in general.

The comparative percentage of drugs is no indication of the efficacy of those drugs. The portion of the molecule that has a pharmacologic effect may be a very small fraction of the over-all part of that molecule. The rest of it may have no toxic and no pharmacologic significance.

In saying that one drug is effective in one-percent concentration and that another drug has that same effect in five-percent concentration is no indication of the relative practical value of those two drugs. There is no reason why the five-percent drug cannot be used as well as the one-percent drug.

The important thing is, what is the relation of the pharmacologic effect as compared with the toxic effect? I don't think that has ever been spelled out in our ordinary testing, and we ought to have some unit of measurement in evaluating new drugs that would incorporate the safe dose of a drug that may be used as a function of the pharmacologic effect.

It is possible that a drug in five-percent concentration may actually be much less toxic than the one that has a one-percent concentration. Therefore, from the practical point of view it may be a more beneficial drug.

It seems to me that the relationship of pharmacologic to toxic effect is surprisingly disregarded in favor of the over-all figure of just a simple percentage.

DR. ABRAHAM: May I say just a word on that? What you say is true. The reports from the drug company are that these particular drugs have a very low lethal dose, a low toxicity from a general injection and absorption point of view.

In point of percentages, in some eyes I used one drop, in other eyes three drops, and sometimes even six drops. The effectiveness was definitely proportionate to the number of drops used.

STUDIES IN ANTIBIOTIC ANTAGONISM AND SYNERGISM*

THE COMBINED ACTION OF PENICILLIN AND CHLOROMYCETIN IN VITRO AND IN INTRAOCULAR STAPHYLOCOCCAL INFECTIONS

JOHN C. LOCKE, M.D.

Montreal, Canada

Exogenous intraocular infections require early and intensive antibacterial therapy, since the fate of the eye may be determined during the first 24 hours. During the time required for the identification of the offending organisms and for the *in vitro* determinations of their antibiotic sensitivities, it would seem advisable to employ a combination of chemotherapeutic agents, as suggested by von Sallmann.¹

In a previous communication,² the local use of a mixture of penicillin and streptomycin was recommended. That these two drugs are indeed mutually helpful has since been generally borne out.³⁻⁵ Some investigators have shown an actual synergism[†] between them, the combined effect being greater than a mere summation of individual drug effects.⁶⁻⁹

Penicillin¹¹⁻¹⁵ and streptomycin[‡] can be

* From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons. This study was supported by the Knapp Memorial Foundation and was included in a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Medical Science, Columbia University. Read in part at the 21st scientific meeting of the Association for Research in Ophthalmology, Inc., Chicago, June 11, 1952.

† With regard to the definition of terms such as "synergism," "additive effect," and so forth, I am in agreement with H. W. Florey,¹⁰ who states: "Since antibiotics act in a highly selective manner on the bacterial cell and can only do so under particular conditions of environment and metabolism, any combined action by which the two together act better than either alone is inevitably an intricate matter. Expressions such as 'synergism,' 'potentiation,' and 'additive effect' come to have less and less meaning as the elaborate nature of the mechanisms involved is appreciated better."

In all subsequent passages in this paper, these terms will only be used in the most general sense, to refer merely to any enhancement of antibacterial effect. Similarly the term "antagonism" is to be taken to include any diminution of such effect of one antibiotic by another.

given together, by subconjunctival injection, in higher concentrations than other presently available antibiotics. Because of the restriction of the total fluid volume that can be injected subconjunctivally, the addition of a third antibiotic to this mixture would only serve to reduce its antibacterial activity.

It would seem advisable, however, to reinforce the local therapy with some type of systemic therapy. Penicillin,¹⁶⁻²⁵ streptomycin,²⁶ and aureomycin^{27, 28} do not enter the ocular tissues readily when given systemically. The sulfonamides enter with greater ease,²⁹⁻³⁵ but are inhibited in pus.

Chloramphenicol possesses neither of these disadvantages. Leopold's studies³⁶ have shown that it enters the ocular tissues in therapeutic concentrations even following oral administration, and reaches still higher concentrations after intravenous injection.

It has a broad antibacterial spectrum,³⁷⁻⁴⁷ is relatively nonirritating to the gastrointestinal tract,⁴¹⁻⁴³ is stable,^{36, 37, 39} and relatively inexpensive. These factors should serve to make chloromycetin a valuable systemic adjunct to local therapy.

These experiments seemed indicated when two papers, published early in 1950 by Jawetz and his co-workers,^{8, 48} reported an

‡ No observations were found in the literature regarding the tolerance of the tissues to subconjunctival injections of streptomycin. I have, on several occasions, injected up to 125,000 µg. of streptomycin, combined with 250,000 units of penicillin, in a total volume of 0.5 cc. of distilled water, at 12-hour intervals, for up to eight injections, in human patients, with no undue reaction of the tissues. (The addition of 0.10 to 0.15 cc. of two-percent novocaine to this mixture renders the treatment less painful. This should be drawn into the syringe *after* the antibiotic solution and injected immediately since, if it is allowed to mix with the penicillin, precipitation occurs.)

antagonism of penicillin action by chloromycetin. In the first of these,⁸ it was observed that chloromycetin interfered with the bactericidal action of penicillin in vitro on many strains of enterococci. The second paper⁴⁸ reported an antagonism of penicillin by chloromycetin in vivo in the treatment of highly fatal experimental infections in mice caused by beta hemolytic streptococci.

The purpose of this study was to investigate further the antagonistic and/or synergistic relationships between penicillin and chloromycetin, and particularly to determine the significance of these in the treatment of exogenous intraocular staphylococcal infections.

The in vitro techniques were used to investigate the more basic aspects of the problem. These were supplemented by in vivo studies carried out on experimentally infected rabbit eyes.

The test organisms used throughout were strains of *Staphylococcus aureus*, isolated from human conjunctivas.

Since the beginning of this work, the observations of Jawetz and co-workers on penicillin-chloromycetin antagonism have been extended,^{9, 49-51} and similar interferences with the action of penicillin have been reported for aureomycin, terramycin,^{52, 53} and the sulfonamides.⁵⁴ As a result, clinicians have been warned against the use of untried antibiotic combinations.⁵⁵

IN VITRO EXPERIMENTS

To demonstrate antagonism of one antibiotic by another, by in vitro techniques, it seemed desirable to use strains of test organisms which did not already need high concentrations of the antibiotics in question for their inhibition. On the other hand, to show synergistic or additive phenomena, the opposite appeared to be true.

With this in mind, eight strains of *Staphylococcus aureus* were first tested for their in vitro sensitivities to penicillin and chloromycetin. Three strains were found which had intermediate degrees of sensitivity to each antibiotic. These required 7.5 μ g. per

cc. of chloromycetin and amounts varying from 0.075 to 0.15 units per cc. of penicillin for their in vitro inhibition.

Two methods of approach were used: (1) A serial dilution-visible turbidity technique, and (2) a serial dilution-colony count technique.

For each experiment, a fresh solution of crystalline sodium penicillin G. was first prepared in normal saline. The chloromycetin, on the other hand, was made up as a stock solution (1.0 mg. per cc., in normal saline) and after being sterilized by Seitz filtration, was kept in the refrigerator (6°C.). A fresh stock solution was prepared every two weeks. Subsequent dilutions of the antibiotics were made in broth.

The media used throughout were heart infusion broth and agar (Bacto-Difco).

I. SERIAL DILUTION—VISIBLE TURBIDITY EXPERIMENTS

The criterion for inhibition of an organism by the antibiotic mixture in question was the absence of visible turbidity in the broth tubes after 48 hours of incubation at 37°C.

Strain Hynes. Preliminary sensitivity tests showed that this strain of *Staphylococcus aureus* was inhibited in broth by 0.15 units per cc. of penicillin, but not by 0.10 units per cc., and by 7.5 μ g. per cc. of chloramphenicol, but not by 5.0 μ g. per cc.

In the experiment, four rows of five tubes were set up—the tubes of each row containing 0.0, 0.025, 0.05, 0.10, and 0.15 units per cc. of penicillin, respectively, in a volume of 1.8 cc. of broth (table 1).

In the first of these rows, penicillin was the sole antibiotic present; the second row contained, in addition, 2.5 μ g. per cc. of chloromycetin; the third row contained 5.0 μ g. per cc., and the fourth row contained 7.5 μ g. per cc. of chloromycetin. In this way, concentrations of penicillin and chloromycetin, which were just above and below those required for inhibition of this strain, were combined.

TABLE 1
VISIBLE TURBIDITY OF BROTH CULTURES OF STRAIN HYNES WHEN THE ORGANISMS ARE
EXPOSED TO VARYING CONCENTRATIONS OF PENICILLIN AND CHLORAM-
PHENICOL ALONE AND IN COMBINATION

Chloramphenicol Concentration (μ g. per ml.)	Concentration of Penicillin (units per ml.)				
	0.0	0.025	0.05	0.10	0.15
0.0	++*	++	++	+	—
2.5	++	++	+	—	—
5.0	++	—	—	—	—
7.5	—	—	—	—	—

* ++ Indicates moderate to dense visible turbidity after 48 hours' incubation at 37°C.

+ Indicates slight visible turbidity after 48 hours.

— Indicates no visible turbidity.

Each tube was inoculated with 0.2 cc. of a 10^{-2} dilution of an 18-hour broth culture. The tubes were incubated at 37°C. for 48 hours and then examined for visible turbidity. The experiment was repeated and the results were the same in both instances.

Results (table 1). Bacterial growth was again inhibited by 0.15 units per cc. of penicillin alone, and not by 0.10 units per cc.; by 7.5 μ g. per cc. of chloramphenicol alone, and not by 5.0 μ g. per cc.

The addition of inhibitory or subinhibitory amounts of chloramphenicol did not interfere with the ability of penicillin to prevent visible bacterial growth when this antibiotic was present in its minimal inhibitory concentration (0.15 units per cc.).

On the other hand, when chloromycetin, in an amount which was just insufficient to inhibit growth (5.0 μ g. per cc.), was added to subinhibitory concentrations of penicillin (0.025, 0.05, and 0.10 units per cc.), visible turbidity was prevented in all three tubes.

Less than half the inhibitory concentration of chloramphenicol (2.5 μ g. per cc.), when combined with 0.10 units per cc. of penicillin (itself not inhibitory), prevented visible turbidity at 48 hours. The same concentration of chloromycetin lessened the degree of turbidity when combined with 0.05 units per cc. penicillin, and had no effect that could be determined by this method when combined with 0.025 units per cc. penicillin.

Strain Margolli and Strain Slade. Similar experiments with the two other strains of

Staphylococcus aureus produced results of the same nature.

Comment

These experiments failed to demonstrate any antagonism between penicillin and chloromycetin, but did demonstrate an additive effect between the two drugs in that concentrations of each drug, which by themselves failed to inhibit growth, when combined, resulted in mixtures that were inhibitory.

It must be pointed out, however, that serial dilution experiments such as these, where the criterion of antibiotic activity is the presence or absence of visible turbidity, give information only about the *bacteriostatic* powers of the drug or drug combination. No information concerning the rate or degree of *bactericidal* action of the drugs can be deduced.

From the experiments described above, it can be concluded that the *bacteriostatic* power of a penicillin-chloromycetin combination is greater than that of either drug alone. To determine the effect of combining the two drugs on *bactericidal* action, it is necessary to do colony counts of organisms exposed to various concentrations of the antibiotics, alone and in combination, at varying time intervals following inoculation.

This has been stressed by the experiments of Jawetz and his associates.⁵⁴ Failure to understand this explains in part the divergence of conclusions reached by different workers, in earlier experiments, regarding

the effects in vitro of combining penicillin with the sulfonamides.^{6, 58-68}

II. SERIAL DILUTION—COLONY COUNT EXPERIMENTS

From a study of Table 1, it is seen that four different combinations of results occurred, depending on the concentration of the antibiotics used in combination:

1. An inhibitory concentration of one antibiotic combined with an inhibitory concentration of the other to give a mixture which was inhibitory (for example, 0.15 units per cc. penicillin with 7.5 μ g. per cc. chloromycetin).

2. An inhibitory concentration of one antibiotic combined with a noninhibitory concentration of the other to give a mixture which was inhibitory (for example, 0.15 units per cc. penicillin with 5.0 μ g. per cc. chloromycetin).

3. A noninhibitory concentration of one antibiotic combined with a noninhibitory concentration of the other to give a mixture which was inhibitory (for example, 0.10 units per cc. penicillin with 5.0 μ g. per cc. chloromycetin).

4. A noninhibitory concentration of one antibiotic combined with a noninhibitory concentration of the other to give a mixture which was noninhibitory (for example, 0.025 units per cc. penicillin with 2.5 μ g. per cc. chloromycetin).

In the serial dilution-colony count experiments which follow, each of these different combinations of results was investigated.

Technique. In each experiment, four broth samples were simultaneously inoculated and studied. These contained: (1) No drug (broth control culture); (2) penicillin alone; (3) chloromycetin alone; and (4) a combination of penicillin and chloromycetin in the same concentrations. The total volume of each sample, including the inoculum, was 10.0 cc.

The same three strains of *Staphylococcus aureus* were used as in the earlier serial dilution-visible turbidity experiments.

Where one or both drugs were used in subinhibitory (partially bacteriostatic) concentrations, the bacterial inoculum consisted of 1.0 cc. of a 10^{-2} dilution of an 18-hour broth culture, containing $10^6/10^7$ organisms. However, where the two drugs were used in inhibitory (bactericidal) concentrations, it was thought advisable to increase the inoculum, and accordingly, 0.5 cc. of an undiluted 18-hour broth culture, containing $10^8/10^9$ organisms, was used.

All cultures were incubated at 37°C.

At intervals, aliquots were removed from the test mixtures, and the numbers of viable organisms determined by serial dilution and plate count.

In a final experiment, colony counts were made after exposure of the test organism to bactericidal concentrations of the two antibiotics, alone and in combination, where the exposure was: (1) To chloramphenicol alone for one hour before the penicillin was added; (2) to penicillin alone for one hour before the chloramphenicol was added; and (3) to both drugs at the same time.

Results. Antibiotic concentrations, which, in visible turbidity experiments, were inhibitory (after 48 hours), were found, in the colony count experiments, to have a bactericidal effect (tables 2, 6, 7, and 8; figs. 1, 4, 5, and 6).

While the ultimate effect of subinhibitory concentrations was always that of partial bacteriostasis only (tables 3, 4, 5, 6, and 7; figs. 2, 3, 4, and 5), with the higher of these an initial transient bactericidal effect was observed.

The results of the colony count experiments may be conveniently classified in groups to represent all possible combinations of the above phenomena:

1. A bactericidal concentration of one antibiotic combined with a bactericidal concentration of the other (table 2; fig. 1).

2. A partially bacteriostatic concentration of one drug combined with a partially bacteriostatic concentration of the other: (a) Where no initial bactericidal effect is present

TABLE 2

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN MARGOLLI TO BACTERICIDAL CONCENTRATIONS OF PENICILLIN (1.0 UNIT PER ML.) AND CHLORAMPHENICOL (25 μ G. PER ML.) ALONE AND IN COMBINATION

	Number of Viable Bacteria per ml.		
	At Time of Inoculation	17 Hours after Inoculation	40 Hours after Inoculation
Control (no drug)	20,000,000	400,000,000	1,500,000,000
Penicillin	20,000,000	50,000	2,000
Chloramphenicol	20,000,000	1,000,000	80,000
Mixture	20,000,000	7,000,000	800,000

for either (table 3; fig. 2); (b) where an initial bactericidal effect is present for one or both drugs (tables 4 and 5; fig. 3).

3. A bactericidal concentration of one drug combined with a partially bacteriostatic concentration of the other (tables 6, 7; figs. 4 and 5).

Control experiments indicated that a two-fold or greater difference in the calculated populations of simultaneously inoculated samples could be considered as significant.

A. EXPOSURE OF ORGANISMS ($10^7/10^8$ per ml.; strains Margolli, Hynes, and Slade) to bactericidal concentrations of penicillin (1.0 unit per ml.) and chloramphenicol (25 μ g. per ml.) alone and in combination.

All three strains showed similar results. Only strain Margolli is tabulated (table 2; fig. 1).

In every case, while the effect of the mixture on the organisms remained a bactericidal one, this was consistently and significantly less than that of penicillin or chloromycetin alone at all time intervals tested (17 to 46

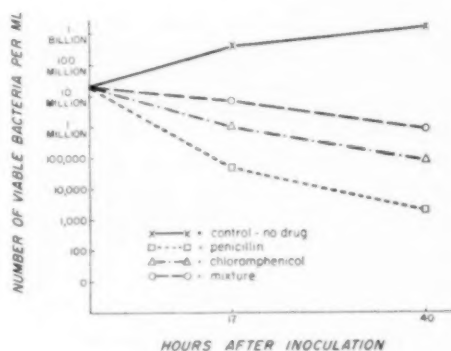


Fig. 1 (Locke). Graphic presentation of data in Table 2.

hours after inoculation).

The magnitude of the differences varied from 2.3 to 11-fold when compared to chloramphenicol, and from 140 to 42,000-fold when compared to penicillin.

B. EXPOSURE OF ORGANISMS ($10^5/10^6$ per ml.; strains Margolli and Hynes) to partially bacteriostatic concentrations of penicillin

TABLE 3

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN MARGOLLI TO PARTIALLY BACTERIOSTATIC CONCENTRATIONS OF PENICILLIN (0.025 UNITS PER ML.) AND CHLORAMPHENICOL (2.5 μ G. PER ML.) ALONE AND IN COMBINATION, WHERE NO EARLY BACTERICIDAL EFFECT IS PRESENT FOR EITHER DRUG

	Number of Viable Bacteria per ml.		
	At Time of Inoculation	7 Hours after Inoculation	26 Hours after Inoculation
Control (no drug)	446,000	145,000,000	416,000,000
Penicillin	446,000	60,000,000	236,000,000
Chloramphenicol	446,000	10,500,000	182,000,000
Mixture	446,000	1,000,000	21,000,000

TABLE 4

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN MARGOLLI TO PARTIALLY BACTERIOSTATIC CONCENTRATIONS OF PENICILLIN (0.05 UNITS PER ML.) AND CHLORAMPHENICOL (5.0 μ G. PER ML.), ALONE AND IN COMBINATION, WHERE AN EARLY BACTERICIDAL EFFECT FOR ONE DRUG (PENICILLIN) IS PRESENT

	Number of Viable Bacteria per ml.		
	At Time of Inoculation	7 Hours after Inoculation	24 Hours after Inoculation
Control (no drug)	400,000	1,500,000	500,000,000
Penicillin	400,000	6,200	4,000,000
Chloramphenicol	400,000	1,000,000	100,000,000
Mixture	400,000	272,000	2,400

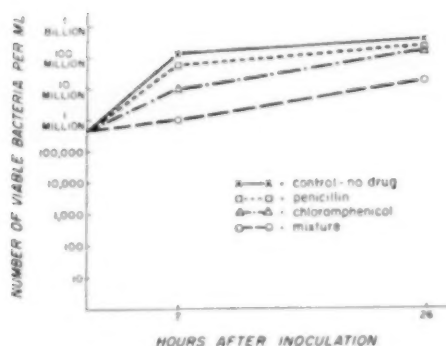


Fig. 2 (Locke). Graphic presentation of data in Table 3.

(0.025 units per ml.) and chloramphenicol (2.5 μ g. per ml.) alone and in combination, where no early bactericidal effect is present for either drug

Both strains showed similar results. Only strain Margolli is tabulated (table 3; fig. 2).

In each case, while the effect of the mixture on the organism remained a bacteriostatic one, this was consistently and significantly greater than that of penicillin or chloramphenicol alone at both time intervals tested (seven and 26 hours after inoculation).

The magnitude of the differences varied from 8.7 to 26.4-fold when compared to chloramphenicol, and from 3.4 to 60-fold when compared to penicillin.

C. EXPOSURE OF ORGANISMS (400,000 per ml.; strain Margolli) to partially bacteriostatic concentrations of penicillin (0.05 units

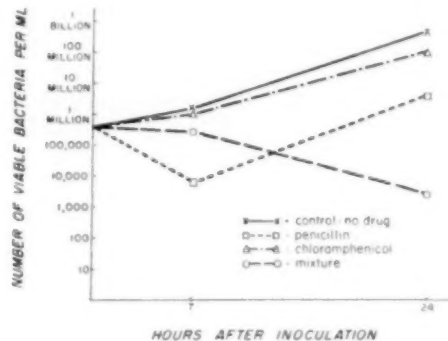


Fig. 3 (Locke). Graphic presentation of data in Table 4.

per ml.) and chloramphenicol (5.0 μ g. per ml.) alone and in combination, where an early bactericidal effect for one drug (penicillin) is present (table 4; fig. 3).

Chloramphenicol was only partially and weakly bacteriostatic throughout.

At seven hours after inoculation, the mixture showed a bactericidal effect (272,000 viable organisms) which was considerably less than the initial bactericidal effect of penicillin alone (6,620 organisms).

By 24 hours following inoculation, however, the bactericidal effect of the mixture was greater (2,400 organisms), while that of the penicillin alone had not been maintained (4,000,000 viable organisms).

D. EXPOSURE OF ORGANISMS (458,000 per ml.; strain Hynes) to partially bacteriostatic concentrations of penicillin (0.05 units per ml.) and chloramphenicol (5.0 μ g. per ml.)

TABLE 5

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN HYNES TO PARTIALLY BACTERIOSTATIC CONCENTRATIONS OF PENICILLIN (0.05 UNITS PER ML.) AND CHLORAMPHENICOL (5.0 μ G. PER ML.), ALONE AND IN COMBINATION, WHERE AN EARLY BACTERICIDAL EFFECT FOR BOTH DRUGS IS PRESENT

	Number of Viable Bacteria per ml.			
	At Time of Inoculation	7 Hours after Inoculation	15 Hours after Inoculation	41 Hours after Inoculation
Control (no drug)	458,000	90,000,000	170,000,000	488,000,000
Penicillin	458,000	12,380	400,000	10,000,000
Chloramphenicol	458,000	80,000	800,000	1,200,000
Mixture	458,000	77,200	560	4

alone and in combination, where an early bactericidal effect for both drugs is present (table 5)

At seven hours following inoculation, the bactericidal effect of the mixture (77,200 viable organisms) was significantly less than that of penicillin alone (12,380 organisms), and about the same as for chloramphenicol alone (80,000 organisms per cc.).

At 15 and 41 hours following inoculation, however, continuation of the bactericidal action of the mixture had almost sterilized the culture (560 organisms at 15 hours; four viable organisms at 41 hours), while the bactericidal action of each antibiotic alone had not been maintained (1,200,000 viable organisms in the case of chloramphenicol; 10,000,000 organisms in the case of penicillin).

E. EXPOSURE OF ORGANISMS (strain Hynes) to a bactericidal concentration of one drug and a partially bacteriostatic concentration of the other, alone and in combination. (a) Penicillin bactericidal (0.15 units per ml.); chloramphenicol bacteriostatic (4.5 μ g. per ml.)—(400,000 organisms per ml. at time of inoculation) (table 6; fig. 4)

Chloramphenicol was only partially bacteriostatic throughout (970,000 organisms at seven hours after inoculation; 752,000 organisms per ml. at 24 hrs.; and 19,000,000 viable organisms at 48 hours following inoculation).

At seven hours after inoculation, the mixture showed a bactericidal effect (30,400

organisms), which was significantly less, however, than that of penicillin (3,080 viable organisms). While the ultimate effect of both the mixture and the penicillin was sterilization of the culture, this occurred sooner with the penicillin alone. (b) Penicillin bacteriostatic (0.075 units per ml.) with early bactericidal effects; chloramphenicol bactericidal (7.5 μ g. per ml.)—(400,000 organisms per ml. at time of inoculation) (table 7; fig. 5).

At seven hours after inoculation, the mixture showed a bactericidal effect (73,000 viable organisms per ml.) which was greater than that for chloramphenicol alone (236,000) but less than that of the initial and temporary bactericidal effect of penicillin alone (1,000 organisms).

By 17 and 44 hours following inoculation, however, the bactericidal effect of the mixture and of the chloramphenicol had increased (still maintaining a very similar quantitative relationship between them), while that of the penicillin had not been maintained (8,500,000 organisms).

F. NUMBER OF VIABLE STAPHYLOCOCCI (strain Hynes) present following exposure of an 18-hour culture to bactericidal concentrations of penicillin (2.0 units per ml.) and chloramphenicol (25.0 μ g. per ml.), alone and in combination, when the organisms are exposed to

Mixture 1—to chloramphenicol for one hour before the penicillin is added

Mixture 2—to both drugs at the same time

TABLE 6

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN HYNES TO A BACTERICIDAL CONCENTRATION OF PENICILLIN (0.15 UNITS PER ML.) AND A PARTIALLY BACTERIOSTATIC CONCENTRATION OF CHLORAMPHENICOL (4.5 μ G. PER ML.), ALONE AND IN COMBINATION

	Number of Viable Bacteria per ml.			
	At Time of Inoculation	7 Hours after Inoculation	24 Hours after Inoculation	48 Hours after Inoculation
Control (no drug)	400,000	100,000,000	400,000,000	—
Penicillin	400,000	3,080	0	0
Chloramphenicol	400,000	970,000	752,000	19,000,000
Mixture	400,000	30,400	220	0

Mixture 3—to penicillin for one hour before the chloramphenicol is added (table 8; fig. 6)

The number of viable organisms in each sample immediately following inoculation was 22,000,000 per cc.

The bactericidal effect of each of the mixtures was significantly less than that of penicillin alone (32,200 viable organisms). (Initial population of each sample as noted above: 22,000,000 organisms/cc.)

It was least where the organisms had been exposed to chloramphenicol first (*Mixture 1*: 10,000,000 viable organisms); somewhat greater when they were exposed to both antibiotics at the same time (*Mixture 2*: 2,840,000 organisms); and greatest when they were exposed to the penicillin for one hour before the addition of the chloramphenicol (*Mixture 3*: 324,000 organisms). The bactericidal effects of *Mixtures 1* and *2* were significantly less than that of chloramphenicol alone (334,000 organisms); that of *Mixture 3* was almost the same.

Comment

The colony count experiments confirm the conclusion drawn from the visible turbidity experiments that the *bacteriostatic* power of a penicillin-chloromycetin combination is greater than that of either drug alone. In every instance where partial bacteriostasis occurred from the use of either drug alone, this was greater for the mixture (tables 3, 4, and 5; figs. 2 and 3).

When one of the antibiotics showed an

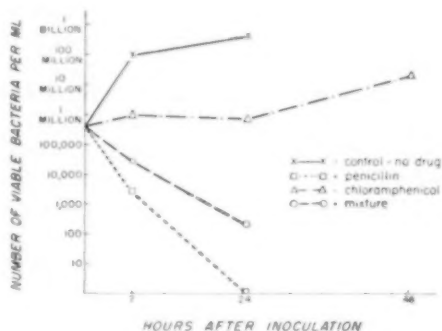


Fig. 4 (Locke). Graphic presentation of data in Table 6.

initial, though transient, bactericidal effect, the mixture proved bactericidal throughout and an extreme difference in the number of viable organisms ultimately resulted (tables 4 and 5; fig. 3).

On the other hand, in every instance in which a consistently *bactericidal* effect was obtained from the use of either drug alone, this was diminished when the two were combined (tables 2 and 8; figs. 1 and 6).

Where the bactericidal action was transient, the antibiotic antagonism was likewise transient (tables 4, 5, and 7; figs. 3 and 5).

The antagonism was most marked when the organisms were exposed to chloromycetin for one hour before the penicillin was added, and least marked when exposed to penicillin for one hour before the addition of chloromycetin (table 8; fig. 6). Jawetz and his associates have recently reported a similar finding.⁵⁰

TABLE 7

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN HYNES TO A PARTIALLY BACTERIOSTATIC CONCENTRATION OF PENICILLIN (0.075 UNITS PER ML.) AND A BACTERICIDAL CONCENTRATION OF CHLORAMPHENICOL (7.5 μ G. PER ML.), ALONE AND IN COMBINATION

	Number of Viable Bacteria per ml.			
	At Time of Inoculation	7 Hours after Inoculation	17 Hours after Inoculation	44 Hours after Inoculation
Control (no drug)	400,000	15,000,000	200,000,000	420,000,000
Penicillin	400,000	1,000	120,000	8,500,000
Chloramphenicol	400,000	236,000	8,220	140
Mixture	400,000	73,000	700	40

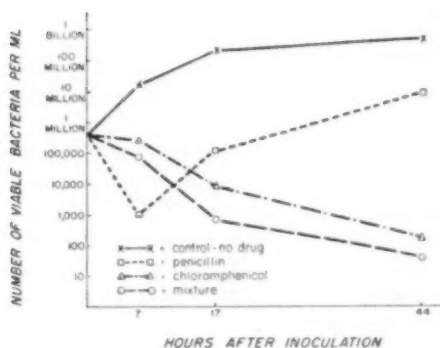


Fig. 5 (Locke). Graphic presentation of data in Table 7.

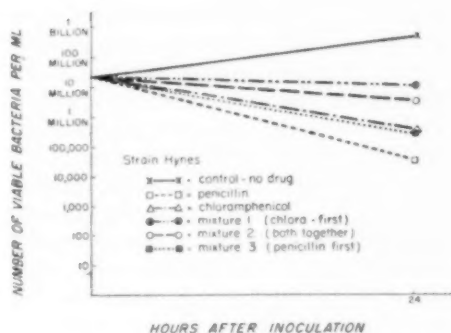


Fig. 6 (Locke). Graphic presentation of data in Table 8.

In no instance was the antagonism of one antibiotic by the other sufficient to change a bactericidal effect into a partially bacteriostatic one. The interference remained at all times merely one of degree.

The interference with the bactericidal

action of penicillin by chloromycetin was greater and more consistent than was the reverse. The former occurred in all eight possible instances, the reverse action in four out of six possible times. It must be noted that penicillin was generally used in the more

TABLE 8

NUMBER OF VIABLE STAPHYLOCOCCI PRESENT FOLLOWING EXPOSURE OF AN 18-HOUR CULTURE OF STRAIN HYNES TO BACTERICIDAL CONCENTRATIONS OF PENICILLIN (2.0 UNITS PER ML.) AND CHLORAMPHENICOL (25 μ G. PER ML.) ALONE AND IN COMBINATION, WHEN THE ORGANISMS ARE EXPOSED: (1) TO CHLORAMPHENICOL FOR ONE HOUR BEFORE THE PENICILLIN IS ADDED, (2) TO BOTH DRUGS AT THE SAME TIME, AND (3) TO PENICILLIN FOR ONE HOUR BEFORE THE CHLORAMPHENICOL IS ADDED

	Number of Viable Bacteria per ml.	
	At Time of Inoculation	24 Hours after Inoculation
Control (no drug)	22,000,000	400,000,000
Penicillin	22,000,000	32,200
Chloramphenicol	22,000,000	334,000
Mixture (1)—Chlora. first	22,000,000	10,100,000
Mixture (2)—Both together	22,000,000	2,840,000
Mixture (3)—Peni. first	22,000,000	324,000

highly bactericidal concentrations. Jawetz did not observe antagonism of chloromycetin by penicillin, only the reverse. This is apparently the first demonstration of this phenomenon.

When a bactericidal concentration of one antibiotic was combined with a bacteriostatic concentration of the other there was a lessening of the effect of the former and an enhancement of the action of the latter, the total effect of the mixture remaining a bactericidal one (tables 6 and 7; figs. 4 and 5).

Jawetz and Speck⁴⁸ pointed out that "interference with the action of one antibiotic by another could conceivably take place in one of three ways: (a) the two drugs could interact with one another in some physical or chemical process, so that the resulting complex was of lesser chemotherapeutic efficacy; (b) the two drugs might compete with one another for 'receptors' on the susceptible bacterial cells . . . and through mass action, the less effective drug might thus interfere with the more potent one; (c) one drug might so change developmental characteristics or properties of the infecting microorganisms that their susceptibility to other agents is greatly diminished."

The results of our experiments eliminate the first two of these as possible mechanisms. With respect to the third possible mechanism, however, it has been generally shown that the more favorable the medium for bacterial growth, the more rapid the rate of killing by penicillin.⁶⁷⁻⁷¹ Conversely, conditions that retard the growth of bacteria, reduce the rate of killing by penicillin.^{68, 72, 73} Jawetz's hypothesis⁵⁰ that interference with the bactericidal action of penicillin by chloromycetin may be a manifestation of the latter phenomenon is supported by the results of our experiments.

While these experiments, in part, serve to confirm the findings of Jawetz and his co-workers of an antagonism existing between penicillin and chloromycetin under certain circumstances, their greater importance and originality lie in demonstrating and

emphasizing the additive or synergistic relationships that may also exist between the two drugs and in clarifying events in the borderline area between these two phenomena.

In the *in vivo* experiments which follow, an attempt was made to determine which of these two phenomena was likely to be the more important, clinically, in the treatment of intraocular staphylococcal infections.

IN VIVO EXPERIMENTS

TECHNIQUE

The same technique of inoculation was used as in our previous study,² 0.05 cc. of inoculum being injected into the anterior chamber of rabbit eyes after making a linear incision in the anterior lens capsule and cortex with the hypodermic needle (30-gauge).

Staphylococcus aureus, strain Hynes, was used throughout.

Preliminary inoculations were first made with varying dilutions in normal saline, of 18-hour broth cultures of this strain, to determine the dilution that would give the most satisfactory test lesion.

It was also necessary to determine the approximate concentrations of the two antibiotics, best suited for these experiments. For the demonstration of antagonism of penicillin action by chloromycetin, it was desirable to use the lowest concentration of penicillin which would be therapeutically effective in a majority of eyes, and to combine with this, the highest concentration of chloromycetin, which when used alone would be just insufficient to control the infection in the majority of eyes.

For the demonstration of an additive effect between the two antibiotics, it was desirable to use such concentrations as would be just insufficient to produce good results, except in a minority of eyes treated.

The antibiotics were applied, alone and in

combination, to the experimentally infected eyes by corneal iontophoresis* (cathode on the eye; current at 1.6 ma.), after local anesthesia with 0.1-percent nupercaine, commencing four to five hours after inoculation. The applications were for five minutes, twice daily, for four to five days.

Forty-one rabbits (82 eyes) were used.

At first, the rabbits were inoculated and treated in groups of four (eight eyes). In any such group, two eyes were left untreated, two received penicillin alone, two received chloromycetin alone, and two a mixture of the antibiotics in the same concentrations. Later, as a definite trend in the results became apparent, additional eyes were inoculated and treated with either penicillin alone or with the mixture, in order to allow for a more rapid and significant comparison.

A slight digression was made from the main course of the experiment when six eyes were injected subconjunctivally with 0.5 cc. of cortisone (25 mg. per cc.), immediately prior to inoculation, and the results compared to the control eyes and to the antibiotic-treated eyes.

*For the purpose of these experiments, iontophoresis was a convenient method of applying both drugs simultaneously. If the two drugs were to be given clinically, however, as stated in the introduction, the subconjunctival route would be recommended for penicillin (with or without the addition of streptomycin, adrenaline, and/or novocaine) and the systemic route (oral or intravenous) for chloromycetin.

TABLE 9

TREATMENT OF EXPERIMENTAL INTRAOCULAR STAPHYLOCOCCAL INFECTIONS STRAIN HYNES: IONTOPHORESIS TWICE DAILY USING PENICILLIN, (4,000 UNITS PER ML.), AND CHLOROMYCETIN, (2.5 MG. PER ML.)

Treatment	No. of Eyes	Results	
		Good	No Effect
Chloromycetin	8	4	4
Penicillin	12	9	3
Penicillin-Chloromycetin	12	9	3
Controls	8	0	8

RESULTS

Inoculation of the eyes with a 10^{-2} dilution of *Staphylococcus aureus*, strain Hynes, produced purulent intraocular infections which were too rapidly destructive to respond satisfactorily to any therapy tried. Inoculation with 10^{-4} dilution produced mild self-limited infections in all eyes. Neither of these lesions was suitable for a comparative evaluation of different antibiotic solutions.

Inoculation with a 10^{-3} dilution of the culture, however, produced lesions which when untreated, invariably developed suppurative panophthalmitis, but, when adequately treated, did not progress (tables 9 and 10). Here, there occurred a clearcut difference in end results between the control and unsuccessfully treated eyes on the one hand and the successfully treated eyes on the other (figs. 7 and 8).

The combination of antibiotic concentrations used to investigate possible antagonism of penicillin effect by chloromycetin were: crystalline sodium penicillin G, 4,000 units per cc.; chloromycetin, 2.5 mg. per cc. Table 9 shows the results of treatment with these concentrations, alone and in combination, of 40 infected rabbit eyes.

Good results were obtained in four out of eight eyes treated with chloromycetin alone, in nine out of 12 eyes treated with penicillin alone, and in nine out of 12 eyes treated with the mixture of the two. Suppurative panophthalmitis developed in the eight control

TABLE 10

TREATMENT OF EXPERIMENTAL INTRAOCULAR STAPHYLOCOCCAL INFECTIONS STRAIN HYNES: IONTOPHORESIS TWICE DAILY USING PENICILLIN (2,000 UNITS PER ML.), AND CHLOROMYCETIN, (1.75 MG. PER ML.)

Treatment	No. of Eyes	Results	
		Good	No Effect
Chloromycetin	8	2	6
Penicillin	10	3	7
Penicillin-Chloromycetin	10	9	1
Controls	8	0	8
Cortisone	6	0	6

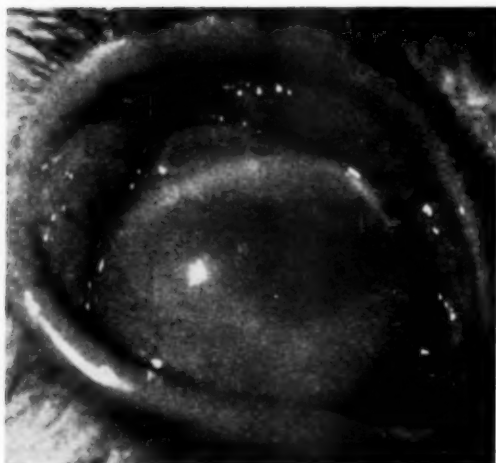


Fig. 7



Fig. 8

Figs. 7 and 8 (Locke). Results of treatment using penicillin and chloromycetin, alone and in combination. (Fig. 7) Control eye, showing severe suppurative panophthalmitis. (Fig. 8) Eye benefited by treatment.

eyes, and in the eyes not benefited by treatment.

The combination of antibiotic concentrations selected to investigate possible additive effect was: crystalline sodium penicillin G, 2,000 units per cc.; chloromycetin, 1.75 mg. per cc. Table 10 shows the results of treatment with these concentrations, alone and in combination, of 36 infected rabbit eyes.

Good results were obtained in two out of eight eyes treated with chloromycetin alone, in three out of 10 eyes treated with penicillin alone, and in nine out of 10 eyes treated with the mixture. Suppurative panophthalmitis developed in the eight control eyes, and in the eyes not benefited by treatment.

Pretreatment by subconjunctival injection of cortisone had no observable effect on the course of the infection in any of the six eyes so treated (table 10). All progressed to severe suppurative panophthalmitis at about the same rate and to the same degree as the control eyes.

COMMENT

The results of these *in vivo* experiments

should be interpreted cautiously, for the following reasons:

(1). Only two combinations of concentrations of the antibiotics were tested, and only one route of administration investigated. Because the accumulation of significant data by this method of approach is costly and time consuming, it was not considered profitable to extend it further.

(2). No data are available on which of the two antibiotics enter the anterior chamber first, when both are given by iontophoresis, or (if they enter together) which is the first to reach its peak concentration at the bacterial site. Table 8 indicates that these are important considerations.

(3). It is not known how the penetration of penicillin through the cornea, in iontophoresis, is affected by the addition of chloromycetin. Von Sallmann,¹ using sulfacetamide and penicillin, found approximately the same concentrations in rabbit aqueous after iontophoresis with solutions containing both their sodium salts, as after iontophoresis with solutions containing the respective salt alone.

In his other experiments,²³ however, using penicillin alone, he measured far greater amounts in the aqueous when distilled water was used as a solvent, rather than 0.9-percent sodium chloride solution. Transient damage to the corneal epithelium, due to hypotonicity of the bathing fluid, was found to be the main factor in the increased penetration.

In our experiments, no antagonism by chloromycetin of the beneficial effects of penicillin on experimental infections in rabbit eyes could be demonstrated. The concentration of penicillin, which by itself was just enough to produce good results in a majority of eyes, was equally effective when combined with the concentration of chloromycetin, which, when used alone, was just insufficient to control the infection in a majority of eyes (table 9).

On the other hand, when the antibiotics were combined in concentrations which by themselves were just unable to bring about a therapeutic effect (except in a minority of eyes), the proportion of good results was significantly higher than that seen after the use of each individual drug (table 10).

The results of these studies therefore suggest that when penicillin is given locally in *effective* concentrations, in intraocular staphylococcal infections, the interference with its bactericidal action by chloromycetin (observed *in vitro*) may not be of practical significance. But when it is given in *sub-optimal* concentrations, the enhancement of its bacteriostatic action by chloromycetin may be of considerable value.

SUMMARY

1. *In vitro*, serial dilution-colony count experiments demonstrated that the antibacterial effect of penicillin-chloromycetin combinations, against three strains of *Staphylococcus aureus*, may be greater or less than that of either drug alone, depending upon the concentration of the antibiotic used and the antibiotic sensitivity of the organism.

2. An enhanced effect occurred when

partially bacteriostatic concentrations of each antibiotic were combined. This was confirmed by serial dilution-visible turbidity experiments. The greatest enhancement of antibacterial effect occurred when one of the drugs showed an initial though transient bactericidal effect.

3. In every instance in which a consistently *bactericidal effect* was obtained from the use of either antibiotic alone, this was diminished when the two were combined. Where the bactericidal action was transient the antibiotic antagonism was likewise transient.

The antibiotic antagonism noted was most marked when the microorganisms were exposed to chloromycetin for one hour before the penicillin was added, and least marked when exposed to penicillin for one hour before the addition of chloromycetin.

In no instance was the antagonism of one antibiotic for the other sufficient to change a bactericidal effect into a partially bacteriostatic one. The interference remained at all times one of degree.

The interference with the bactericidal action of penicillin by chloromycetin was greater and more consistent than the reverse.

4. When a *bactericidal concentration of one antibiotic was combined with a bacteriostatic concentration of the other*, there was a lessening of the effect of the former and an enhancement of the action of the latter, the total effect of the mixture remaining a bactericidal one.

5. In the treatment of experimental intraocular staphylococcal infections in rabbits, by corneal iontophoresis, no antagonism by chloromycetin of the beneficial effects of penicillin was demonstrated. When the antibiotics were applied in suboptimal concentrations, the proportion of controlled infections was significantly higher than after the use of each drug alone.

6. Pretreatment by subconjunctival injection of cortisone had no observable effect on the course of the infection.

1414 Drummond Street.

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DISCUSSION

DR. IRVING H. LEOPOLD (Philadelphia): Dr. Locke has reported on a carefully done, meticulous study. He has taken an extremely complex problem and has tried to clarify the issue for us.

There are many factors which have to be considered in dealing with combinations of antibiotics. Dr. Locke has noted in testing one or two strains of organisms that, when combinations of antibiotics are used such as penicillin and chloromycetin, they are not always antagonistic as suggested by others but may be synergistic.

One wonders what would happen if a mixture of organisms were used, such as gram-positive with gram-negative organisms, and whether the combination of penicillin and chloromycetin would be superior to chloromycetin alone or penicillin alone.

Clinically, it is with mixtures of organisms that we are most likely to want to use a combination. Often, one does not know the responsible infecting agent. Then it is desirable to use an antibiotic or antibiotic combination which has a wide antibacterial spectrum.

Among the many subjects of interest in Dr. Locke's talk was the one of dosage. Dr. Locke pointed out that the combination of low dosage of chloromycetin and low dosage of penicillin produced a greater bacteriostatic effect than either agent alone in the same dosage. Experience in the era of the sulfonamides taught the importance of hitting the infecting organism with large doses of sulfonamides over a long period of time. As we become acquainted with the newer antibiotics, it appears that this may not be desirable. It may be better to hit an organism with a large dose of penicillin once, rather than to repeat it at frequent intervals throughout any 24 hour period. It, perhaps, may be better to do the same thing with chloromycetin.

The evidence available at the present time does not tell us any definite facts along this line, but it is suggestive that large doses of penicillin given at infrequent intervals is successful therapy for many infections. More data are needed concerning dosage schedules. More data of the type compiled by Dr. Locke are needed concerning combinations of antibiotics.

From the information presented by Dr. Locke, it is evident that the combination of penicillin and chloromycetin properly employed is not always antagonistic but may be additive or even synergistic in combined action against specific gram-positive organisms.

However, this does not mean that all strains of staphylococci or streptococci respond in the same way to these combinations.

Further detailed similar studies along this line by Dr. Locke will cast more light on this complicated subject.

DR. SAMUEL V. ABRAHAM (Los Angeles): My comment may be out of order, but it isn't clear to me whether or not the experiment considered this particular point:

If you take the same dosage of penicillin, for example, that you are considering in your experiment, and combine it with a similar dosage of chloromycetin in that particular experiment, and judge the results on the basis of the two, it does not seem to be statistically quite accurate that you should compare the results of the two together with the results of either one unless the amount of either one is of equivalent amount.

For instance, if you found a certain percentage of penicillin effective, and added a certain amount of chloromycetin that was effective, and judged the result of the two together, as compared to each individually, it does not seem to be quite accurate. You should compare the results of the two with results of using an increased amount of either one of them. Otherwise, the good results may be considered due to additive factors rather than synergistic factors.

DR. JAMES H. ALLEN (New Orleans): I would like to compliment Dr. Locke on a very beautifully designed and well-executed experiment. I had the privilege of looking over his protocols before the meeting, and it seems to me that there could be very little improvement on the design and execution of the experiments.

The one question that does arise, however, is the practicability of this experiment in view of the

diminishing susceptibility of staphylococci to penicillin. The thing we have experienced has been a very rapid drop in susceptibility of staphylococci to penicillin. Some years ago as high as 95 percent of our strains of staphylococci were susceptible to penicillin. About two years ago the percentage of our ocular strains had dropped to around 60 percent that were susceptible to penicillin, and at the present time it is less than 40 percent.

Our infectious disease laboratory, which checks susceptibility of staphylococci isolated from other sources has had a similar experience.

Therefore, I wonder if Dr. Locke intends to imply that a combination of penicillin and chloramphenicol would be more effective than chloramphenicol alone in those cases in which penicillin alone is ineffective?

DR. LOCKE (Montreal): In the treatment of an intraocular exogenous infection, the fate of the eye is usually determined within 24 to 48 hours after making the diagnosis, and therefore we are forced to administer immediately the most effective possible antibacterial therapy. This therapy has to be commenced before the identities of the organisms involved and their antibiotic sensitivities are known.

Three years ago, the local use of a mixture of penicillin and streptomycin in the treatment of such infections was recommended (Locke, J. C.: Experimental studies with antibiotics: Bacitracin, streptomycin, penicillin, and antibiotic mixtures in intraocular infections with penicillin-resistant staphylococci. *Am. J. Ophthalm.*, 32:135 (June Part II) 1949) and I still feel that such a combination, given subconjunctivally, is the local treatment of choice.

We have given 1,000,000 units of penicillin subconjunctivally, and, as mentioned in the body of the paper, streptomycin can also be given subconjunctivally in very high concentrations. I know of no other antibiotics that can be given locally in such concentrations.

I am in agreement with Dr. Allen concerning the increase of resistance to penicillin by strains of staphylococci. However, the definition of resistance to an antibiotic is an arbitrary one. Effective action is dependent, among other things, upon the concentration of the antibiotic that can be obtained in the tissue where the infection lies.

Using these massive local concentrations of penicillin, amounts sufficient to inhibit most strains of staphylococci can still be obtained in the ocular tissues of the anterior segment.

Further, Jawetz has shown a true synergistic effect when penicillin and streptomycin are used together, and he has also shown that adding streptomycin to penicillin more or less erases any antagonism of penicillin action by chloromycetin.

Concerning the theory as to how the chloromycetin interferes with the bactericidal action of penicillin, it is known that anything that interferes with the multiplication of organisms interferes with the bactericidal action of penicillin. It is felt that chloromycetin interferes in this manner.

In answer to Dr. Abraham, we were interested in comparing the two drugs, using the same dosages alone and in combination, because in clinical practice this is the way they would be used; the dosage of either drug would not be reduced when used in combination.

I wish to thank Dr. Leopold for his discussion.

STUDIES ON THE EFFECT OF NORADRENALINE AND ADRENALINE ON THE EYE*

L. VON SALLMANN, M.D., M. P. MEYERS, M.D., AND B. PILLAT, M.D.

New York

The concept of the nature of the adrenergic nerve mediators has undergone several changes since Loewi¹ and Cannon² first interpreted the results of their fundamental work on neurohumoral transmission in the

sympathetic nervous system. The history of these changes has been reviewed repeatedly in recent years³⁻⁶ and in the present report will be referred to only insofar as may be required for an understanding of the experimental approaches and their results.

In 1946, von Euler⁷ demonstrated in an extract of the splenic nerves of cattle the presence of an adrenergic substance which showed the characteristics of noradrenaline, the primary amine which differs from adrenaline by the absence of the N-methyl

*From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital. This study was supported by the Knapp Memorial Foundation and the Snyder Ophthalmic Foundation. Dedicated in sincere devotion to Prof. Karl Lindner on the occasion of his 70th birthday.

group. A few years later Peart⁸ (1949), working in Gaddum's laboratory, provided experimental evidence that in the main noradrenaline, and not adrenaline, was released *in vivo* when the splenic nerves of cats were stimulated. The existence of two adrenergic transmitters in extracts of the adrenal medulla, suspected in 1948 by Holtz and Schümann,⁹ was proven chemically by Goldenberg and associates¹⁰ (1949) and by Bergström¹¹ and co-workers.

From this and other investigations emerged the now generally held opinion that two substances, noradrenaline and adrenaline, serve neurohumoral transmission in the sympathetic nervous system and in organs innervated by adrenergic nerves. These compounds differ in many of the biologic responses they elicit. With reference to the eye, for example, adrenaline, has been shown to be more effective than noradrenaline in dilating the normal pupil of the cat and in causing retraction of its nictitating membrane.

Highly relevant to the study of intraocular pressure are the effects of adrenaline and noradrenaline on the general circulation. In contrast to the over-all vasodilation induced by adrenaline, changes in the blood pressure indicate that noradrenaline has in general a vasoconstrictor effect. Goldenberg and co-workers¹² have observed these effects in man, and observations on the cat have also revealed that noradrenaline in small quantities produces regularly a rise in blood pressure, whereas adrenaline exerts chiefly a vasodepressor effect.

The present investigation was undertaken in an effort to relate the effect of physiologic amounts of these two hormonal substances on the blood pressure to their effects on the intraocular pressure. For this purpose a technique was elaborated which allowed the manometric registration of changes in the intraocular pressure, and at the same time the registration of changes in the general blood pressure, in ranges of sensitivity greatly exceeding those obtained in previously reported work.

MATERIALS AND METHODS

Previous investigators found that the cat was best suited for the differentiation of the actions of adrenaline and noradrenaline. Our series of more than 80 experiments were therefore restricted to observations on cats. Mature young animals weighing from 2.4 to 3.0 kg. were used. General anesthesia was induced by interperitoneal injection of chloralose in doses of from 55 to 70 mg. per kg., and blood clotting was prevented by the intravenous administration of heparin sodium (10 mg./kg.) prior to the insertion of the cannula. One femoral artery served for cannulation.

The metal cannula was provided with a fine polyethylene tube long enough to record the blood pressure in the iliac artery or in the abdominal aorta. The femoral vein of the other side was cannulated in a similar way by means of a lumbar puncture needle with locking stilet; this was used for the intravenous injection of the pharmacologic agent.

For the transmission of pressure changes in the eye, a 30-gauge needle was introduced into the anterior chamber and attached by an adaptor and lead tubing to the microphone in the bridge circuit of the Sanborn electro-manometer. Prior to the insertion of the needles into the anterior chamber, in one series of experiments, the cervical sympathetic nerve was prepared and placed on small electrodes for electrical stimulation.

By means of the two-channel instrument of Sanborn and Company, which consists of two separate electromanometers with A.C. amplifiers and rectifiers and D.C. amplifiers, connected with a twin-viso recording unit, the simultaneous recording of two pressures in ranges of widely different magnitude could be achieved. A description of this electromanometer was presented by Dr. DuPont Guerry, III,¹³ in his report of a study carried out in this laboratory.

With this apparatus the speed of writing could be varied and the sensitivity of trans-

mission modified in each channel separately so that pressures and pressure changes at different levels, as for example, variations in blood pressure and intraocular pressure, were directly comparable with respect to both time and extent.

Records obtained by the use of a sensitive transducer showed in the tracing changes of 1.0 mm. in height for a pressure change of 0.1 mm. Hg. Moreover, it was possible to write simultaneously, in a high sensitivity range, the intraocular pressures of both eyes, and to record changes in the medium blood pressure by ink-writing with a bellow manometer on an endless belt kymographion. The timer units of the twin-viso apparatus and the kymographion were then interconnected to allow comparison of the three records (fig. 1).

The hydraulic system of the electroma-

nometer, including needle, needle adaptor, and lead tubing, was filled with a solution of sodium chloride (0.9 percent) and tested rigidly for complete absence of air bubbles. When the pressure of both eyes was examined, the needles were inserted symmetrically in the horizontal meridian in the frontal plane, so that the tip of each needle lay in the prepupillary area of the anterior chamber and were held in position by special cannula holders. A lead rod fixed between the cannula holder and its clamp gave some flexibility to the latter and allowed final delicate adjustment in all positions. This step was preceded by accurate leveling of the pertinent parts of the manometer and the head of the animal.

The levo-isomer of noradrenaline in the form of bitartrate monohydrate was used in a 0.1-percent solution from which higher

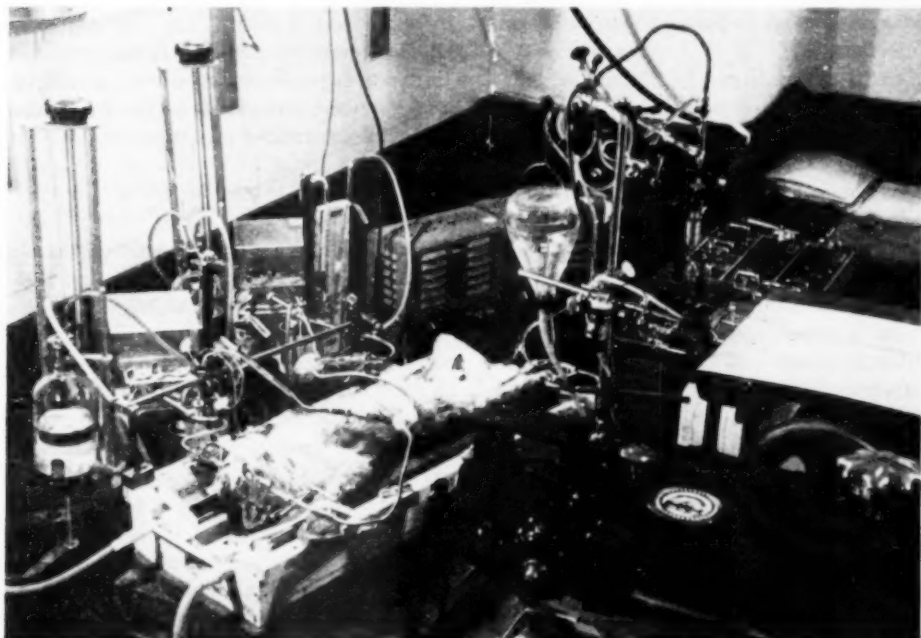


Fig. 1 (von Sallmann, Meyers, and Pillat). Apparatus for simultaneous manometric recording of the pressure in both eyes and in the iliac artery of the cat, showing the needles in the anterior chamber of the animal connected to two electromanometers of Sanborn with rectifiers, A.C. and D.C. amplifiers, and with the twin-viso recording unit. The blood pressure in the shown experiment is synchronized with an ink-writing bellow manometer on an endless belt kymographion.

dilutions were made with a 0.9-percent sodium-chloride solution. Ascorbic acid in an amount of 10 μ g. per cc. of fluid was added for stabilization. Synthetic epinephrine bitartrate powder served for the solutions of adrenaline. Quantities of from 0.1 to 0.4 μ g. per kg. body weight were injected intravenously. In some experiments amounts up to 1.6 μ g. per kg. were used.

After the induction of the hormonal agents through the cannula in the femoral artery, 0.5 cc. of a 0.9-percent solution of sodium chloride was injected by the same route so that the entire amounts of the hormonal compounds would be sure to reach the general circulation. Injections of the sodium-chloride solution were also employed several times during the course of an experiment in order to observe the effect of the incorporated volume of fluid on the pressures studied. A time interval of from three to four minutes was allowed to elapse between injections.

In 10 experiments, the cannula in the femoral vein was connected with an infusion bottle for rigidly controlled drip infusion of noradrenaline and adrenaline. Solutions of 50 μ g. per 50 or 100 cc. of a 0.9-percent solution of sodium chloride or of Ringer solution were made up for this purpose. Amounts of from 10 to 15 μ g. were infused within 10-minute periods.

In 14 experiments the influence of an adrenergic block on the biologic responses to noradrenaline and adrenaline was studied 30 minutes after a slow intravenous injection of dibenamine in an amount of 10 mg. per kg. body weight. For the electrical preganglionic stimulation of the exposed cervical sympathetic nerve (23 experiments), the pulsating direct current of an Electrodyne stimulator was employed for 15 seconds at an output potential of eight volts and a frequency of 10 impulses per second.

In order to study the effect of noradrenaline and adrenaline on the intraocular pressure of eyes sensitized by denervation, the

superior cervical sympathetic ganglion was removed from 15 cats 12 to 90 days prior to the manometric measurements.

RESULTS

The characteristics of manometrically recorded physiologic variations in eye pressure in the form of respiration and pulse waves, which were first clearly demonstrated by Wessely¹⁴ to be dependent upon corresponding rhythmic changes in the blood pressure, were well illustrated by the high-speed writing of the Sanborn twin-viso recording unit. Figure 2 shows these apparently simultaneous changes in blood and eye pressure at both the low speed of 30 mm. per minute and the high speed of 300 mm. per minute.

In experiments performed at high speed, which will be reported in the next paragraph, a minimal lag of about one-tenth of a second was observed between the onset of changes in the blood pressure and the onset of changes in the eye pressure. In the great majority of experiments in which manometric readings were obtained from both eyes, the two curves paralleled each other closely.

EFFECT OF INTRAVENOUS INJECTION OF NORADRENALINE AND ADRENALINE

Intravenous injections of noradrenaline in doses of from 0.1 to 1.6 μ g. per kg. body weight were followed by a simple transient increase of blood and eye pressures. The same quantities of adrenaline gave rise to a biphasic response with the vasodepressor effect usually exceeding by far the pressor effect. The curves representing the increments and decrements in blood and eye pressures resembled each other closely.

In general, a change of 10 mm. Hg in the blood pressure corresponded to a change in the eye pressure of about 1.0 mm. Hg. Occasionally the elevation or drop in the ocular-tension, expressed in percents of the base pressure, were estimated to be greater than those of the blood pressure. The increments usually followed a linear scale when the

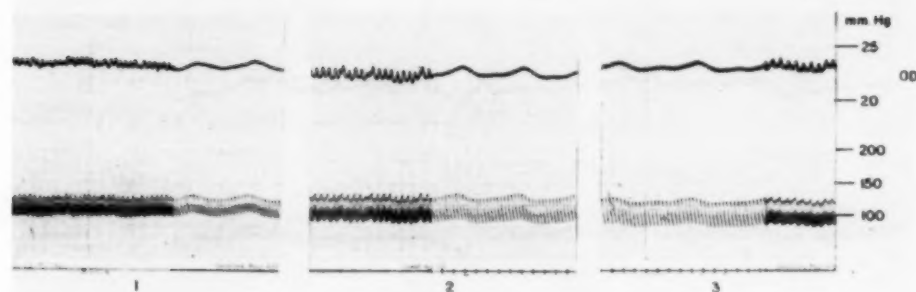


Fig. 2 (von Sallmann, Meyers, and Pillat). Respiratory and pulse waves in the blood-pressure and eye-pressure tracings written at low and high speed. In Figures 2 to 5, six squares correspond to 60 seconds at low-speed writing; six squares equal six seconds at high-speed recording.

doses of the injected compounds were increased according to an arithmetic scale. (fig. 3).

The changes in both pressures produced by small quantities of noradrenaline and adrenaline varied considerably in extent and duration according to the sensitivity of the experimental animal. In young cats, typical responses of 2.0 or 3.0 mm. Hg in the ocular tension were observed often as a result of the intravenous use of as little adrenaline or noradrenaline as 0.1 μ g. per kg. body weight (fig. 4).

In other and particularly in older animals, double this amount, or even more, was necessary to produce similar effects. In sensitive preparations, increases or decreases in pressure up to 5.0 mm. Hg were observed on the eye. The effect of the small quantities of both agents lasted about one minute but was prolonged when amounts of more than 0.4 μ g. per kg. were used.

With the doses of adrenaline and noradrenaline administered in this experimental series, the widths of the lid fissure, the position of the nictitating membrane, and the size of the pupil remained unaltered.

Slowly injected dibenamine (10 mg. per

kg.) abolished the pressor effect of both compounds on the blood and eye pressures but did not influence the vasodepressor effect of the adrenaline.

EFFECT OF DRIP INFUSION OF NORADRENALINE AND ADRENALINE

Drip infusion with solutions of noradrenaline (50 μ g. per 50 or 100 cc. in a 0.9-percent solution of sodium chloride) was adjusted in a manner to secure a rise of blood pressure on a relatively constant level for a period of 10 minutes.

Reflex bradycardia with an increase in pulse amplitude was observed during this time. The record of the intraocular pressure showed a corresponding elevation with pulse waves of greater altitude at a slightly reduced rate per minute. At the termination of the infusion a decline of the eye pressure to the original range paralleled a similar change in the blood pressure.

When adrenalin was infused by slow drip (three experiments), a fall in the intraocular pressure coincided with a fall in the general blood pressure. During the administration of adrenalin, increments in the pulse ampli-

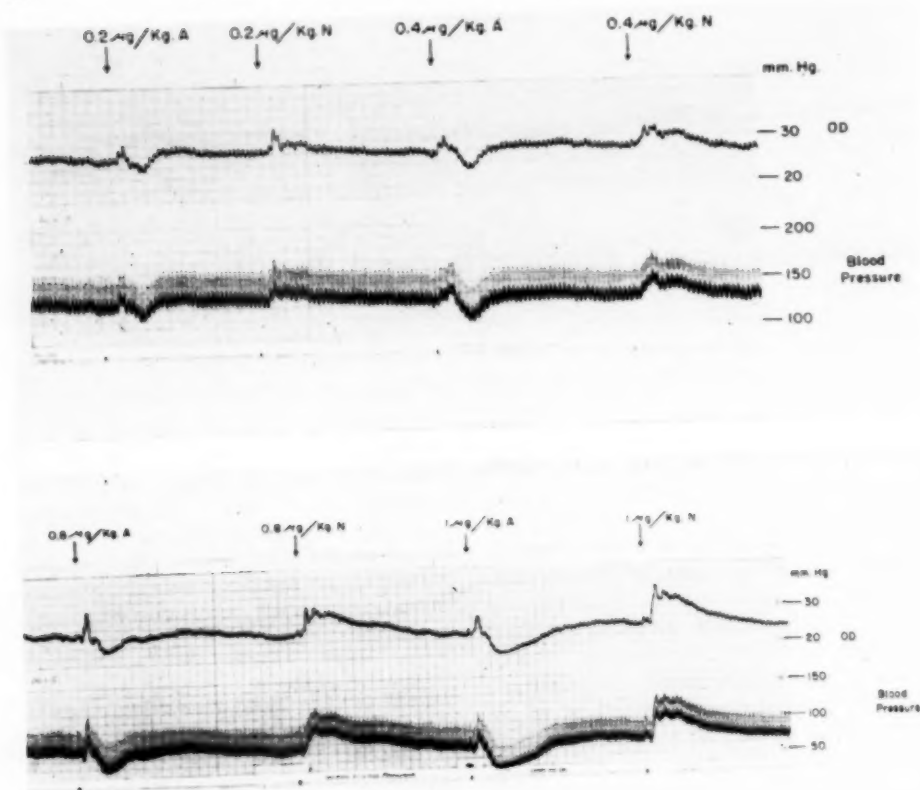


Fig. 3 (von Sallmann, Meyers, and Pillat). Responses of the blood pressure and intraocular pressure to increasing quantities of noradrenaline and adrenaline.

tude without diminution of the pulse rate could be observed in both records.

EFFECT OF PREGANGLIONIC ELECTRIC STIMULATION OF THE CERVICAL SYMPATHETIC CHAIN

Preganglionic electric stimulation of the intact cervical sympathetic chain of one side for 15 seconds evoked a slight increase in the blood pressure. Sympathetic section or crushing of the nerve did not abolish this effect completely.

The intraocular pressure on the non-operated side scarcely responded to this

moderate change in blood pressure. On the homolateral eye the effect of stimulation of the cervical sympathetic chain was indicated by widening of the lid fissure, retraction of the nictitating membrane, and marked or maximal dilatation of the pupil.

At the onset of stimulation the intraocular pressure sometimes rose briefly, slightly, and precipitously, but in 21 of the 23 experiments the main response consisted in a fall in pressure of about 5.0 mm. Hg. This characteristic response lasted about one minute and its curve resembled the curve of the response produced by 0.1 to 0.2 µg. of

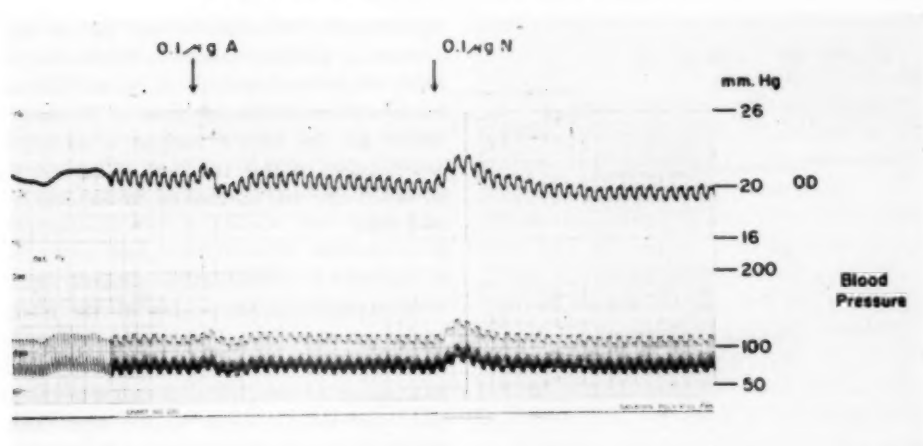


Fig. 4 (von Sallmann, Meyers, and Pillat). Responses of blood pressure and intraocular pressure to noradrenaline and adrenaline in a dose of $0.1 \mu\text{g}$. per kg. at a high sensitivity range.

adrenaline, as illustrated in Figure 5.

In two animals only, did electric pre-ganglionic stimulation result in a rise in eye pressure of about 5.0 mm. Hg for 30 sec-

onds; this was succeeded in both instances by a minimal decline of the tracing below the base pressure (fig. 6).

Cutting or crushing of the nerve cen-

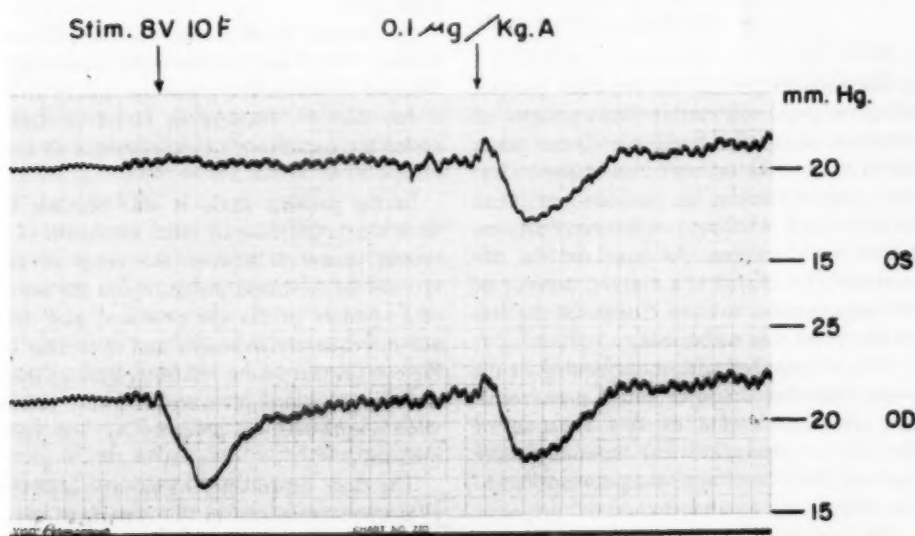


Fig. 5 (von Sallmann, Meyers, and Pillat). Responses of the intraocular pressure to electric stimulation of the left cervical sympathetic chain and to adrenaline, $0.1 \mu\text{g}$. per kg. body weight.

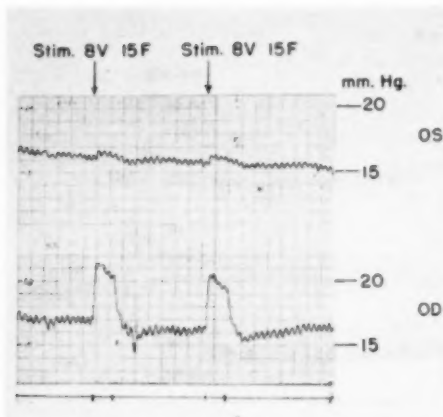


Fig. 6 (von Sallmann, Meyers, and Pillat). Exceptional increase of the intraocular pressure to electric stimulation of the left cervical sympathetic chain.

trally from the site of the electrode modified neither the reading of the resting intraocular pressure nor the reactions to stimulation of the preganglionic fibers.

EFFECTS OF DENERVATION BY REMOVAL OF ONE SUPERIOR CERVICAL SYMPATHETIC GANGLION

The extirpation of the superior cervical ganglion produced certain known signs of sensitization to the hormonal agents when about two weeks or more had elapsed after the ganglionectomy. In response to small amounts (0.1 to 0.2 μ g.) of intravenously injected noradrenaline, the pupil of the denervated eye dilated to a marked degree; on the nonoperated side no change in the size of the pupil was to be seen.

When compared with the widening of the pupil following the injection of noradrenaline, the sensitization of this function of the iris to adrenaline was definitely more marked, the dilatation of the pupil approaching in this case an almost maximal response.

With respect to the manometrically recorded intraocular pressure, no signs of sensitization to noradrenaline or adrenaline could be established in the majority of the

experiments. Occasionally the fall of the intraocular pressure caused by adrenaline in these quantities appeared to be accelerated but less extensive. In only three of 10 experiments did the record suggest a moderate sensitization of this function of the eye to noradrenaline and adrenaline on the denervated side.

DISCUSSION

Manometric measurements of the intraocular pressure in a high sensitivity range made it possible to record, in cats, responses to amounts of noradrenaline and adrenaline that were several times smaller than those necessary to elicit reactions to these compounds in the nictitating membrane and pupil. The advantage of the described techniques in providing a means of recording an important biologic response in the eye much more sensitively than other methods of manometry permit was coupled with the advantage of subjecting the eye to relatively slight trauma and of avoiding with other objectionable features inherent in the older techniques.

As shown by Wessely, Adler, and co-workers,^{14a, b, c} and others many years ago, changes in intraocular pressure appear to be a function of changes in blood pressure under the conditions of experiments of this kind.

In the present study it was possible to show that a brief lag of about one-tenth of a second occurred between the onset of responses in the blood pressure and the onset of responses in the eye pressure, and that not infrequently increases and decreases in the eye pressure were relatively greater than those in the blood pressure when the values were expressed in percents of the base pressure.

The close dependency of variations in the eyes upon variations in the general circulation exclude the possibility that any extraocular factors as, for example, the activity of the smooth muscles of the orbit, play a part in the mechanism of these changes.

There is every indication that the phenomenon is purely vascular in nature.

With regard to the responses of the intraocular pressure to noradrenaline and adrenaline, it should be admitted that the mechanism of this reaction is not clear. Pressor effects caused by vasoconstriction would be expected to lead to a fall in the intraocular pressure, and vasodilatation accompanying vasodepressor effects would be expected to cause an increase in the plethysmographic pressure of the eye.

Since the opposite reactions took place, it could be assumed that the intraocular arteries do not contract sufficiently to prevent a dilatation of the capillary bed as a result of increased blood pressure, and that the fall of the blood pressure overcompensates the effect of local vasodilatation. It could also be assumed that the action of the adrenergic agent extends to the intraocular veins.

It should be stressed that the quantities of noradrenaline and adrenaline which lead to characteristic changes in the intraocular pressure can be considered as falling within a physiologic range. P. Trendelenburg¹⁵ estimated that the suprarenal gland of the cat in general anesthesia secretes 0.2 μ g. of adrenaline per kg. and minute. It was shown in this study that half this amount injected intravenously produced in the same experimental animal a vasodepressor effect accompanied by a marked fall in eye pressure.

There have been no previous reports on the effect of noradrenaline on the intraocular pressure. The experimental results of Wessely,¹⁴ Duke-Elder,¹⁶ and others, pertaining to the effect of systemically introduced adrenaline, cannot be compared with the present work in view of the great difference in dosage and the probability that mixtures of adrenaline and noradrenaline were injected by these investigators.

In contrast to the action of small doses of adrenalin, which have been shown in this study to produce a decrease in intraocular pressure, noradrenalin produces a rise in intraocular pressure when it is administered

in small quantities by the intravenous route.

These observations on the effect of minimal amounts of adrenergic mediators on the eye may add to the understanding of neurohumoral controls of mechanisms which govern the intraocular pressure under physiologic and pathologic conditions.

The experiments in which the compounds were administered by slow intravenous infusion were performed for the purpose of studying the adaptation of the two pressures to the continuously supplied adrenergic agent. The results indicated that within 10-minute periods autoregulatory mechanisms in the eye did not bring about adjustment of the intraocular pressure to the abnormal conditions independent of the status of the general blood pressure.

It has been shown that the noradrenaline-adrenaline ratio varies with the animal species. Burn and Hutcheon,¹⁷ and von Euler,³ arrived at the conclusion that noradrenaline was the predominant chemical transmitter in the sympathetic nervous system of the cat, whereas Gaddum and Kwiatkowski¹⁸ identified adrenaline as the transmitting agent in the ear of the rabbit.

Electrical stimulation of the sympathetic cervical chain in the present series produced a lowering of the intraocular pressure at the homolateral side. The similarity of the tracing in response to this stimulation and to the injection of 0.1 μ g. of adrenaline may suggest that adrenaline should be considered as the neurohumoral transmitter under the conditions of this experiment. There is a distinct possibility, however, that a vasoconstrictor effect on the intraocular vessels upon stimulation of the nerve produced the change in pressure. Other experimental approaches which are now under study will be necessary, therefore, to clarify this point.

Fall in intraocular pressure following electrical stimulation of the cervical sympathetic chain has been described by previous workers, and most recently, in rabbits, by H. Davson.¹⁹ Observations to the contrary (Jaffe²⁰) cannot be properly evaluated be-

cause tonometry was used for the determination of the intraocular pressure. In our series the shape of the curve with exceptional rises indicated that they were caused by contraction of the smooth orbital muscles.

The phenomenon of sensitization of the viscus by denervation was observed in our experiments on the cat in the reaction of the pupil to small amounts of noradrenaline and adrenaline. Burn and Hutcheon¹⁷ found the sensitization greater to noradrenaline than to adrenaline but, under the conditions of the experiments reported here, there was greater sensitization to adrenaline.

At present it remains unexplained why the vascular mechanism leading to changes in the intraocular pressure was only exceptionally sensitized by the preceding removal of the superior cervical ganglion since denervation of other vascular beds has been shown to result in sensitization to the action of various pharmacologic agents.

SUMMARY AND CONCLUSIONS

1. A manometric method of high sensitivity for the immediate comparative determination of blood pressure and intraocular pressure of both eyes has been elaborated. For this purpose the Sanborn twin-viso equipment and a bellow manometer were synchronized.

2. The observations of previous investigators on the close dependency of amplitude and frequency in the rhythmic variations of the eye pressure upon such variations in the blood pressure have been confirmed. A very short lag between the onset of the changes in the blood pressure and in the eye pressure could be measured at high-speed writing.

3. In a study of the effect of small amounts of noradrenaline and adrenaline (from 0.1 to 1.6 μg . per kg. body weight) on the blood pressure and eye pressure of the cat, the pure pressor effect of noradrenaline in the general circulation was expressed in the tracing of the intraocular pressure by a simple rise. The biphasic response of the blood pressure to adrenaline was reflected photographically in the intraocular pressure; the fall in the pressures was the predominant feature.

4. Drip infusion of noradrenaline and adrenaline induced synchronous changes in the records of the blood and eye pressures.

5. Electrical stimulation of the cervical sympathetic chain usually caused a marked fall in intraocular pressure. The resemblance of the decline in the tracing of the eye pressure record to the record produced by the injection of 0.1 to 0.2 μg . of adrenaline conveyed the impression that adrenaline is the chemical mediator liberated to the effector tissue during the stimulation of the supplying nerve, but further experimental evidence is necessary before definite conclusions can be drawn.

6. Unilateral denervation obtained by the removal of the superior sympathetic ganglion sensitized the dilatator of the iris, especially to adrenaline, but, as a rule, the vascular responses which govern changes in intraocular pressure by the action of noradrenaline and adrenaline were unaffected.

635 West 165th Street (32).

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DISCUSSION

DR. DAVID G. COGAN (Boston): I judge, Dr. von Sallmann, that the changes in the intraocular pressure which you note are a mirror of the vascular effects in the eye, and that you don't mean to imply that these measurements indicate any change in the secretory activity or the secretory control of intraocular pressure. Is that correct?

DR. VON SALLMANN: We have no indication that the effects of the small quantities of the compounds used in these acute experiments have any effect on the secretory mechanism.

DR. COGAN: Would you say these are volume changes within the eye that you are recording?

DR. VON SALLMANN: Dr. Cogan, you put your finger on a sore spot. It is not at all easy to ex-

plain these pressure changes since one could argue that vasoconstrictor effects induced by noradrenalin would lead rather to a fall of the intraocular pressure instead of to a rise. In view of the plethysmographic nature of the intraocular pressure, there would seem to be only two possible explanations: (1) That the intraocular arterioles do not contract sufficiently to protect the capillary bed from passive dilatation, or (2) that these adrenergic transmitters act also on the venous part of the circulation as they have been assumed to do on the vasculature of the kidney.

DR. FRANK W. NEWELL (Chicago): I should like to learn if these changes in intraocular pressure take place when increase in the systemic blood pressure is prevented. If so, we could attribute these changes in intraocular pressure to be a reflection of

the general vascular pressure. It has been our experience that intraocular pressure increases when the systemic blood pressure is increased by ligating the aorta and that the intraocular pressure very sensitively shows the general systemic blood pressure.

By preventing an increase in the intra-arterial pressure, one may also prevent an increase in the intraocular pressure. We have been preventing the increase in intra-arterial pressure by passing a large catheter into one of the major arteries and having the blood rise in a column. Under these conditions we have found, although presumably vasoconstriction and vasodilatation occur within the eye, that there is no significant increase in intraocular pressure when the systemic blood pressure does not vary.

The question thus arises with the injection of noradrenalin, if the increase in blood pressure is prevented, is there a change in the intraocular pressure?

DR. VON SALLMANN: Under the experimental conditions, no changes in the intraocular pressure occurred without corresponding changes in the general blood pressure. If a blocking agent such as dibenamine was used, pressor responses were abolished and inhibitory responses preserved in both pressures. We did not have such clear-cut results with ligation of the carotid artery as you apparently have had. It doesn't seem to be easy to arrive at conclusions on the basis of experimental procedures which necessitate complicated manipulations in a small area. However, I would feel at present that the effect of noradrenalin and adrenalin on the eye reflects only changes in the general blood pressure. The percent increase in the base pressure is sometimes greater in the eye than it is in the general circulation.

DR. NEWELL: I think that we are in full agreement that the changes in the intraocular pressure parallel the changes in the systemic blood pressure.

We did not ligate the carotid. That causes too many changes in the blood pressure in the head. But we did ligate the abdominal aorta to cause increase in blood pressure. The pressure within the eye very sensitively followed the change in pressure in the arterial system.

The problem arises then, I think, as to what compensatory mechanism there is within the eye to prevent the development of glaucoma in patients with vascular hypertension.

DR. VON SALLMANN: I mentioned that the slow-drip infusion was carried out for the purpose of studying the adaptability of the mechanisms governing the eye pressure to abnormal conditions; that is, to an increase, for one reason or another, of the pressure in the eye. When the experiment was continued for 10 minutes only, the eye pressure did not seem to adapt itself more quickly to the abnormal conditions than the blood pressure. However,

observations on a preparation over a 10-minute period cannot be expected to explain the relative independence of the intraocular pressure and the general blood pressure as it is observed in patients with general hypertension.

DR. M. A. LAST: May I ask whether you used noradrenalin and adrenalin locally to get an effect on the ocular tension?

Secondly, did you note any pupillary changes at the time you used the injections?

DR. VON SALLMANN: In the present studies we did not use noradrenalin and adrenalin locally, but previous investigators (Gaddum, von Euler, and others) have found noradrenalin much less effective than adrenalin in dilating the cat's pupil.

With respect to the second question, the quantities we used, that is, between 0.1 microgram and 1.6 microgram per kg. body weight, did not produce any noticeable effect on the nictitating membrane, on the position of the eye, or on the pupil so long as we dealt with normal animals. If the eyes were sensitized by ganglionectomy, sensitization to both drugs was observed. Dilatation of the pupil was obtained with 0.1 or 0.2 microgram. In contrast to the findings of other investigators, the sensitization was greater to adrenalin than to noradrenalin.

DR. K. W. ASCHER: I wonder whether it would be possible to take records of the systemic venous pressure during these experiments. This might be indicated because of the assumption of Colomba, some 22 years ago, that increased systemic venous pressure might be responsible for the increase of intraocular pressure.

It might also explain in a certain way the observations reported by Thomassen during the last five years, who, upon studying the aqueous veins of glaucomatous eyes, found very striking differences in filling of the recipient vessels during the period preceding the increase of intraocular pressure, as compared to during the phase preceding a decrease of intraocular pressure.

My question would be whether in these experimental animals systemic venous pressure could be taken. It might be very difficult, under these circumstances, to measure the pressure inside the aqueous veins, but it might be different before and after administration of one or the other drug. At least the systemic venous pressure could be measured.

DR. VON SALLMANN: I quite agree with Dr. Ascher that it would be very difficult to measure the pressure in the aqueous veins with the set-up we have; but even the measurements of the venous pressure in smaller branches would not be easy. Although I do not know whether measurements of the changes of the pressure in the larger veins would really contribute to the solution of the problem, it might be possible to carry out such experiments and we shall certainly make an attempt to do so.

EXPERIMENTALLY INDUCED TOXIC EFFECTS ON STRUCTURE AND FUNCTION OF VISUAL CELLS AND PIGMENT EPITHELIUM*

WERNER K. NOELL, M.D.
Randolph Field, Texas

This is a short report on the retinal effects of two agents in respect to their bearing on problems of retinal pathology. The agents are sodium iodoacetate and sodium iodate. They were employed to analyze the metabolic dependence and electrical manifestation of visual cell function.

The study originates from the discovery that sodium iodoacetate, when administered intravenously in experimental animals, abolishes almost immediately the function of the visual cells.¹⁻³ Depending on the dosage, this effect is either reversible or associated with permanent damage of visual cell structure.

The histologic effect of this agent, which has been described and discussed elsewhere,² appears to simulate the degeneration of visual cells and pigment epithelium as manifested in retinitis pigmentosa. To stress the similarities between the effects of the enzyme poison and the hereditary degenerative disease is the purpose of this presentation.

The experiments with iodoacetate administration were performed on albino rabbits, cats, and rhesus monkeys. The effects of iodate were studied only in albino rabbits. With the least systemic toxicity the following doses produced widespread effects on the retina:

Rabbit—two injections of 20 mg./kg. bodyweight of iodoacetate; cat—two injections of 10 to 12 mg./kg. bodyweight of iodoacetate; monkey—two injections of 30 to 35 mg./kg. bodyweight of iodoacetate; rabbit—one injection of 4.0 to 6.0 cc. of a two-percent iodate solution. All solutions were adjusted to the pH of the blood.

After a variable length of time ranging from 12 hours to six months the responsive-

ness of the eyes to illumination was tested by recording the electroretinogram. At the same time, the steady-potential across the globe was measured and often, as well, its reaction to sodium azide.⁴

In many experiments the exposed retina was also explored by microelectrodes. In rabbits, furthermore, the excitability of the optic nerve to electrical stimulation was tested by applying electrical stimuli to the optic nerve just behind the globe and recording the response potential from the visual cortex.

Subsequently one or both eyes were removed and immediately immersed in Zenker solution. Paraffin or celloidin sections were prepared and stained with hematoxylin-eosin, Heidenhain-phloxine and the Mallory trichrome stain; the latter two stains were not employed routinely. Further details as to the methods employed are given in preceding publications.^{2,4}

In all three species, iodoacetate produced a widespread disappearance of the visual cells.² The character and the distribution of this effect with regard to its application to human pathology is best exhibited by the changes of the monkey's retina. Here, the effect of the agent clearly differentiated between rod cells and cone cells.

In accord with the findings on the visual cell population in rabbit and cat, almost all rod cells completely disappeared within two to four weeks after the injections. Partially degenerated or even preserved in their normal form were only those located within a short distance from the ora serrata. In addition, a few rod cells had variably survived at the edge of the optic disc. Otherwise no remnants of the rod cells were present with the exception of a few, widely scattered, pyknotic nuclei.

The doses of iodoacetate which were able

* From the U.S. Air Force School of Aviation Medicine.

to destroy almost the whole rod cell population were, however, less effective on the cone cells. In the three cases studied, the cone cells were invariably preserved at the macular region up to eight weeks after the injections. Parafoveally, however, they showed degenerative changes which increased in severity with the distance from the macula.

At distances of three to five mm. from the fovea, the outer and inner limbs of the cones had completely disappeared, while the anterior portions of the cone cells had survived. Cone cell degeneration exceeding this change was not observed in the cases studied.

Thus, over the greater part of the retina the cone cell remnants (nuclei and perikaryon) formed a single row of "epithelial" cells located inside the external limiting membrane. Except for the foveal and parafoveal region the cone cells were likewise preserved or less damaged than the majority of their

population in the same areas where the rod cells showed a greater resistance against the effects of the agent. They were invariably better preserved in these areas than the rod cells.

Essentially the same spatial distribution in the susceptibility of rod and cone cells and the same difference between rod cell and cone cell population which the effect of iodoacetate produced in the monkey, is well known to be present in retinitis pigmentosa, as evidenced by the clinical progress of the disease and by the few cases in which the retinas were examined histologically.

In Figure 1, the macular region of two monkeys treated by iodoacetate is compared with a case of retinitis pigmentosa which Leber⁵ illustrated in Figure 179 of his review.

Leber's illustration, which is reproduced at the top of Figure 1, shows a section through

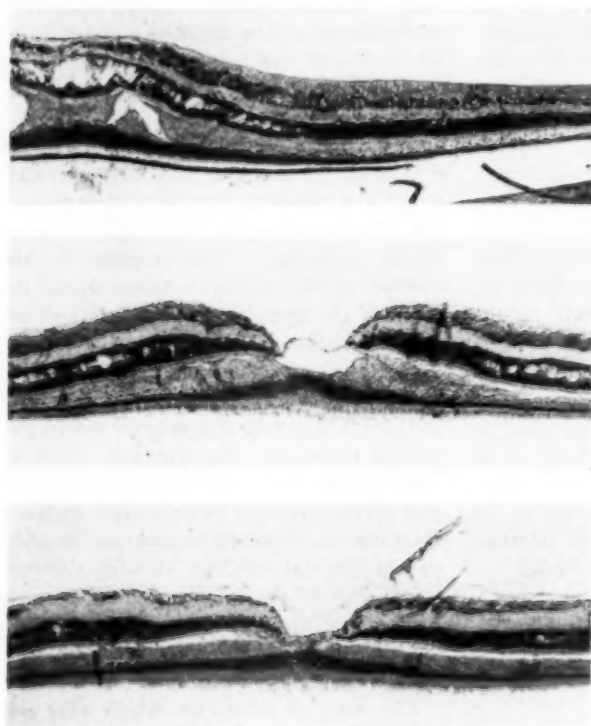


Fig. 1 (Noell). Macular region in retinitis pigmentosa as compared with the effects of iodoacetate in rhesus. (Top) Leber's Figure 179 from a case of retinitis pigmentosa. (Middle) Rhesus monkey six weeks after intravenous iodoacetate administration, hematoxylin-eosin, $\times 90$. (Bottom) Rhesus monkey eight days after intravenous iodoacetate administration, hematoxylin-eosin, $\times 90$.

the retina slightly outside the foveal region. It demonstrates a continuous decline in the width of the outer nuclei layer associated with a progressive reduction in the length of the cone segments with increasing distance from the fovea.

The same is evident in the monkey's retina after treatment by iodoacetate. The sections are cut through the center of the monkey's macula which is less deeply excavated than in humans.⁶ The monkey, from which the section in the middle of Figure 1 was obtained, had received two intravenous injections (hind leg) of iodoacetate of 40 and 30 mg. per kg. bodyweight, respectively, with an interval of 24 hours between the injections. Both doses were administered under Dial anesthesia. The animal was in perfect health thereafter. The eye was removed six weeks after the last injection.

In the other monkey (lower part of Figure 1), a total of 90 mg./kg. bodyweight of iodoacetate had been administered intravenously in three injections during a period of 24 hours without the use of an anesthetic. As a result of another injection eight days after the preceding ones, the monkey suddenly died (eight hours after the injection) due to acute cardiac arrest. The eyes were removed within five minutes after death and immediately fixed in Zenker solution.

The same appearance of the macular region, as illustrated in Figure 1, was also exhibited in our third monkey after a total dose of 80 mg./kg. bodyweight and removal of the eye six and one-half weeks after the first injection.

Examples for the appearance of the cone cells within the foveal and parafoveal region are illustrated in Figure 2. For comparison Leber's Figure 180 is reproduced. Within the fovea, the cone cells are of normal form, as has been reported for all cases of retinitis pigmentosa which were examined at an early stage.

Outside the fovea there is swelling of the inner segments of such degree that the cones seem to take the whole space which had been

occupied by the rods previous to the administration of iodoacetate. There is a progressive reduction in the height of the inner segments until finally (fig. 3) at distances of about five mm. from the fovea all sensory organelles have disappeared.

The cone cells then form an almost continuous row inside the external limiting membrane, occasionally some cells showing short projections through the membrane, as Leber⁵ and Verhoeff¹⁰ described for cases of retinitis pigmentosa.

Retinal areas in cases of retinitis pigmentosa, in which the process has not resulted in the complete destruction of the cone cells, are described to show minimal changes in the pigment epithelium. In Verhoeff's case, the pigment epithelium was always present behind areas in which there were remains of cones. Only in the case of Ascher¹¹ were the pigment cells destroyed in the foveal region though the neuro-epithelium had been preserved.

In the five cases studied by Cogan¹⁵ there was some degeneration and some attenuation of the cells but the epithelium was always present as a monocular membrane with no real hyperplasia or disintegration, despite extensive disappearance of the visual cells.

In the monkeys treated by iodoacetate, where the process invariably spared those portions of the cone cells located inside the outer limiting membrane, the pigment epithelium was preserved throughout. It formed a continuous row of one layer which, if at all, differed from the normal controls by a slightly reduced content of pigment in the midperipheral portions of the retina.

The pigment epithelium was also preserved in rabbits when relatively low doses of iodoacetate had been employed which sufficed to destroy all visual cells except those located at the anterior border of the retina and those close to the optic nerve. Similarly, in cats where iodoacetate likewise tended to affect all visual cells, the complete disappearance of the visual cells over wide areas was not

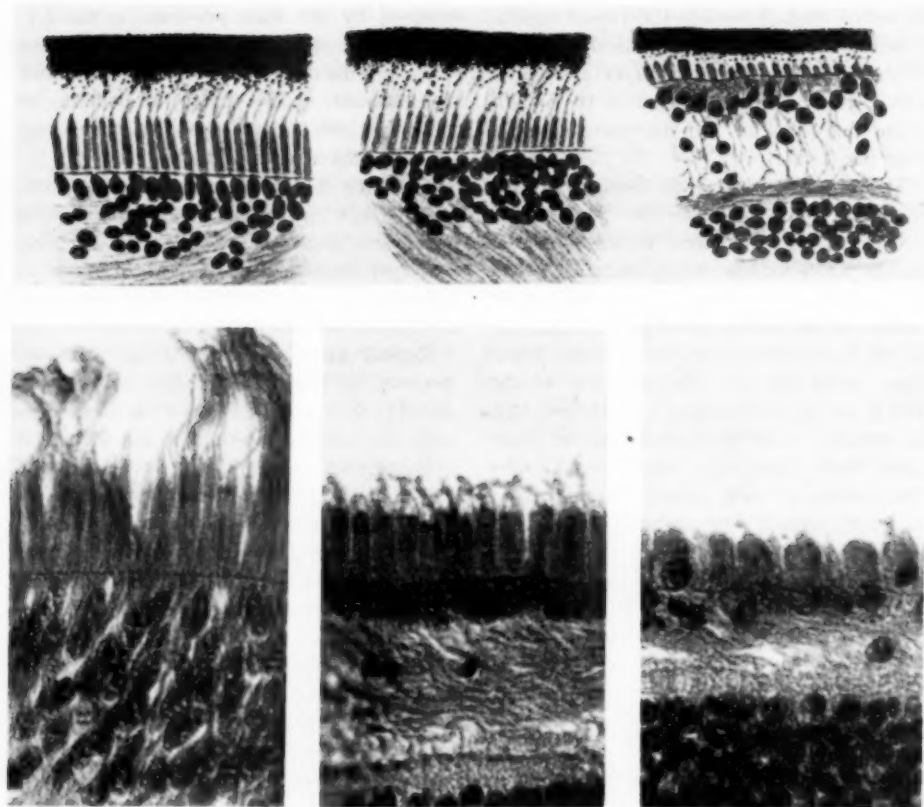


Fig. 2 (Noell). Macular region in retinitis pigmentosa as compared with the effects of iodoacetate on the rhesus. (Top) Leber's Figure 180 of a case of retinitis pigmentosa. (Bottom) Same rhesus retina as middle of Figure 1; from left to right increasing distance from center of fovea. Hematoxylin-eosin, $\times 600$.

obligatorily associated with changes of the pigment epithelium other than a slight reduction in the amount of the pigment enclosed.

Eyes of the same cats, removed at various times after the injections, revealed that, even four months after almost complete disappearance of the visual cells, the pigment epithelium had preserved its normal appearance if it had done so during the first weeks after iodoacetate administration.

These findings do not support Leber's⁸ and Elwyn's¹² assumption that the degenerative and proliferative changes of the pigment epithelium with migration of the pigment

cells into the retina are a result of the degeneration of the neuro-epithelium. If this were the case, the complete destruction of the visual cells over wide areas of the rabbit's and the cat's retina (in these animals both cone cells and rod cells disappeared) should have been associated with changes of the pigment epithelium.

Preservation of the pigment epithelium was invariably associated with an intact outer limiting membrane which was in direct, loose contact with the pigment cells. Also glia reactions were missing in such cases and all inner layers and the framework of the retina had maintained normal appearance.

Amazingly, the degeneration of the visual cells had no effect on the retina as a whole.² We, therefore, must conclude that the retinal gliosis is probably not caused by the stimulatory action of the process of visual cell degeneration nor does it seem justified to assume that gliosis occurs in order to fill the spaces left by the disappearing visual cells. The intraocular pressure must suffice to prevent the development of any unorganized regions within the retina if such regions follow the contours of the retina.

Changes of the pigment epithelium and reactions of the glial elements were, however, observed in rabbit and cat when the dosage of iodoacetate was higher than necessary for the widespread destruction of the visual cells.²

These changes appear to be essentially the same as has been described for retinitis pigmentosa. In both albino rabbit and cat, there was complete disappearance of the epithelium in certain places, in other places it was either preserved in normal form or exhibited various degenerative or proliferative changes. Circumscribed (fig. 4-a) or over wide areas (4-b) it appeared in two or more layers; in other places the pigment cells had multiplied without breaking their row. Many cells contained two nuclei (fig. 4-c);

others were pyknotic. In the cat, additional changes in the amount of the pigment present were apparent.

Large areas of the pigment epithelium were almost free from pigment contrary to normal behavior while the cells themselves had apparently maintained normal morphology. Deposits of pigment within the retina were present in front of places where the pigment epithelium had either disappeared or proliferated and where it normally contained pigment. At regions where the cells had become free of pigment with maintenance of their form and with no sign of proliferation the overlying retina did not show any pigment accumulation.

The distribution of degeneration of the pigment epithelium was a very characteristic one, again reminiscent of retinitis pigmentosa. In any given eye the most severely affected area was located in the peripheral portion of the retina either halfway between the ora serrata and the optic nerve or closer to the ora serrata and occasionally only slightly posterior to the anterior retinal strip where the visual cells showed greatest resistance against the agent.

In these peripheral areas the change in the pigment epithelium could occur in an isolated form, all other portions of the epi-

Fig. 3 (Noell). Rhesus monkey six weeks after iodoacetate administration; same retina as in Figure 2. (Top) From midperipheral region. (Bottom) Short distance from ora serrata. Hematoxylin-eosin, $\times 600$.



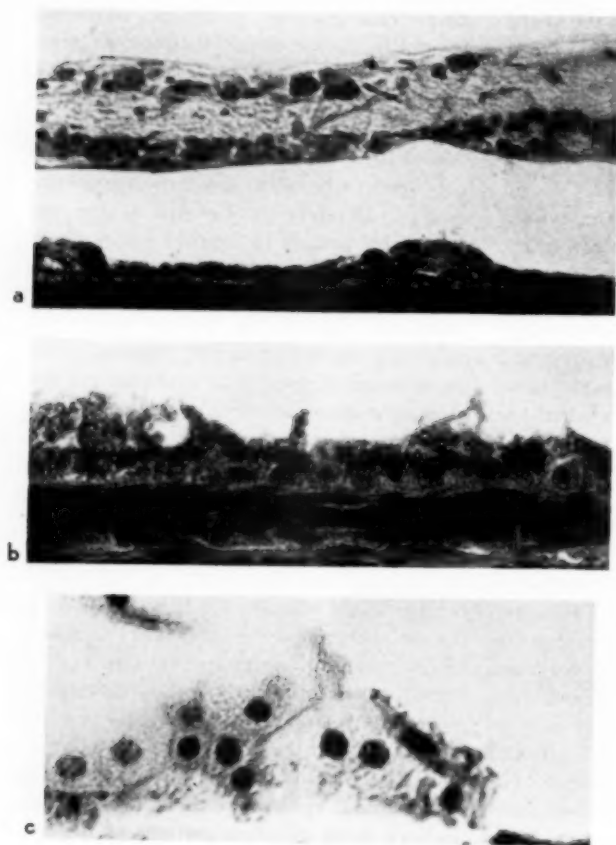


Fig. 4 (Noell). Pigment epithelium after iodoacetate. (Top) Cat, right eye, four months after 22 mg./kg. bodyweight intravenous iodoacetate. Anterior third of retina. Hematoxylin-eosin, $\times 480$. (Middle) Same cat as at top, left eye, six weeks after intravenous iodoacetate; midperiphery. Hematoxylin-eosin, $\times 920$. (Bottom) Albino rabbit, three weeks after 40 mg./kg. bodyweight intravenous iodoacetate, flat section through pigment epithelium. Heidenhain-phloxine, $\times 920$.

thelium showing normal morphology. Likewise, the deposition of pigment within the retina was almost restricted to these regions.

Since it is very improbable that the degenerative and proliferative change of the pigment epithelium occur in response to the disappearance of the visual cells, it must be assumed that iodoacetate affects directly the pigment cells. The resistance of the pigment cell to the agent must then be assumed to be greater than that of rod and cone cells. The same argument seems to hold for retinitis pigmentosa.

If visual cell destruction is not necessarily associated with pigment cell changes, then the cause for these changes in the disease is most probably the same which leads to the

degeneration of the neuro-epithelium—a possibility which to our knowledge was first stated by Verhoeff.¹⁰

The preservation of pigment cells in areas in which the cone cells or their remnants have survived should then be regarded either as accidental or due to a spatially similar distribution of the degree of abnormality of cone cells and pigment cells with the additional assumption that in any given area the degree of cone cell impairment is greater than that of the corresponding pigment cells.

Degeneration of the pigment epithelium in our experiments was almost invariably associated with glia reaction and interruption or disappearance of the outer limiting membrane.² Since these changes in the framework

of the retina were largely dependent on the state of the pigment epithelium, it seems likely that they are partially caused by the degeneration and proliferation of the pigment cells. The character of these reactions which has been described and illustrated in the original publication² is essentially the same as outlined by Leber⁵ and Verhoeff.¹⁰

Structural changes of nervous elements of the inner layers were not observed in any experiment with monkey or cat, though the total width of the remaining retinal layers was slightly reduced as compared with the controls. Never was there any sign of nuclear degeneration.

In the rabbit, where the inner layers are of smaller width than in cat and monkey, distortion of these layers and atrophy of the nervous elements were occasionally encountered several weeks after large portions of the pigment epithelium had vanished and the glia had markedly proliferated.

Bipolar cells and ganglion cells, however, almost invariably were preserved even nine weeks after iodoacetate when the pigment epithelium had survived. Optic nerve excitability to direct electrical stimulation, when tested in rabbits at various times after the injections, was always maintained.

This general preservation of the nervous elements of the retina despite the degeneration of the visual cells and pigment epithelium is regarded as evidence that iodoacetate affects one particular cell process on which neuro- and pigment epithelium depend to a greater extent than the nervous elements. Again there is a general agreement with retinitis pigmentosa.

In Verhoeff's case, the nuclei of the internal nuclear layer were well preserved, though the layer was greatly distorted by the large number of newly-formed Müller fibers. The ganglion cells were somewhat reduced in number outside the macular regions, but still abundant in spite of a duration of blindness for 20 years.

In Ascher's case, the layer of the ganglion cells was more defective and the large cells

were greatly reduced in number. Primary atrophy of the inner layers is assumed by Leber,⁵ but he fails to discuss this point. Atrophy of the optic nerve likewise is stated by Leber but in Verhoeff's, Stock's, and Ginsberg's cases, optic disc and nerve are reported to be normal.

Marked reduction in the caliber of the retinal vessels—a characteristic feature of retinitis pigmentosa—developed with great rapidity within the first two weeks after iodoacetate in all cats and in some of them all retinal vessels finally appeared to be bloodless. In monkeys, the reduction in the caliber of the vessels was slight or moderate. Choroidal changes were not apparent in cat and monkey; in the rabbit, which does not possess a retinal circulation, the choriocapillaries seemed to be reduced in width. No inflammatory reactions were revealed in any case.

An essential phenomenon of retinitis pigmentosa is the extinction of the electroretinogram at an early stage of the disease as was first reported by Karpe.¹³ Complete disappearance of the electroretinogram after iodoacetate was observed in rabbit and cat when the visual cells had disappeared over the whole retina except for a small region close to the ora serrata. Presence of the visual cells at the ora serrata for distances exceeding five mm. was, however, associated with a small electrical response to strong illumination.

The electroretinogram of a monkey six weeks after iodoacetate poisoning is illustrated in Figure 5. It is markedly reduced as compared with the normal electroretinogram recorded with the same magnification and the same technique. Figure 1 (middle), Figure 2, and Figure 3 illustrate the histologic appearance of the same eye.

At the time when the illustrated electroretinogram was recorded, sensory organelles were preserved only in the macular region and close to the ora serrata for a distance up to six mm. In another monkey, a higher amplitude of the electroretinogram was as-

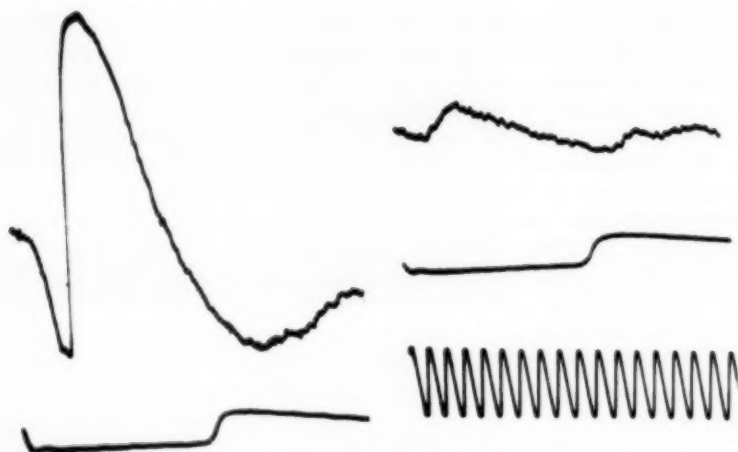


Fig. 5 (Noell). Electrophoretogram in response to a short flash of light as indicated by bottom line. (Left) Normal monkey. (Right) Monkey six weeks after intravenous iodoacetate administration. Both monkeys are in dial anesthesia. Time in 100/sec.

sociated with a better preservation of rod and cone cells in the extreme periphery.

No important differences, therefore, seem to exist between structural and electrophysiologic changes associated with retinitis pigmentosa and the effect of iodoacetate. Certainly the full production of the same changes as in retinitis pigmentosa was achieved in no species exposed to effects of iodoacetate.

The absence of a cone population in rabbit and cat comparable to that of primates, makes it impossible to simulate convincingly retinitis pigmentosa in these species since the most significant property of the disease is the difference with which cones and rods are affected. Nevertheless, visual cell nuclei with a chromatin appearance typical for the cones of lower vertebrates appeared to resist the effects of iodoacetates in these species for a longer period of time than typical rod cells.²

On the other hand, iodoacetate had little direct and indirect effects upon the pigment epithelium of the monkey.

The systemic toxicity of the poison forbade the use of higher doses which, as indicated by the findings in rabbit and cat, would probably have resulted in more severe effects.

As to changes in the pigment epithelium, my conclusions, therefore, have to rely on the findings with the two other species.

In spite of these experimental difficulties, it seems to emerge very clearly that the order in which iodoacetate affects the various cellular constituents of the retina is the same with which the disease progresses. Moreover, for any cell population of the retina—be it the cones, the rods, or pigment cells—the spatial distribution of susceptibility to iodoacetate is apparently the same as in the case of the disease.

Thus, the metabolic property which is responsible for the selective effectiveness of iodoacetate must be distributed over the various retinal population in the same manner as that property which determines degeneration due to a particular genetic abnormality. These two properties may not be related at all, but it seems to me that there is great chance that they are related or even that they are one and the same.

On the latter assumption, the hypothesis is entertained that the metabolic process with which iodoacetate interferes is genetically controlled and that the genetic abnormality in retinitis pigmentosa impairs the mainte-

nance of this process as iodoacetate does by a probably different mechanism of action.

The experimental evidence, discussed on various occasions,¹⁻³ points to the glycolytic process as the site of action of iodoacetate. On the basis of the hypothesis advanced above, impairment of the same process is held responsible for the degeneration in retinitis pigmentosa.

The selective effects of iodoacetate on the retina become particularly evident when compared with those of sodium iodate for which Sorsby¹⁴ has claimed a close relationship with retinitis pigmentosa. The effect of sodium iodate differs in many respects from the action of iodoacetate though both agents impair the same outermost layers of the retina. Both produce degeneration of the neuro-epithelium leading to disappearance of

the rods and both induce changes of the pigment epithelium.

Iodate affects the rod cell population, however, in a different manner than iodoacetate; there is no sparing of the areas close to the ora serrata which on the contrary are often most severely affected. The effect of iodate on the pigment epithelium is furthermore of considerably greater magnitude than that of iodoacetate when compared on the basis of equal effectiveness on the neuroepithelium.

In addition, iodate produces variably circumscribed infiltration of the choroid by round cells and occasionally collections of such cells are found in the space between the external limiting membrane and the chorioidea (figs. 6-b and 6-c).

Iodate affected the pigment epithelium with greatest effectiveness. In the doses used,

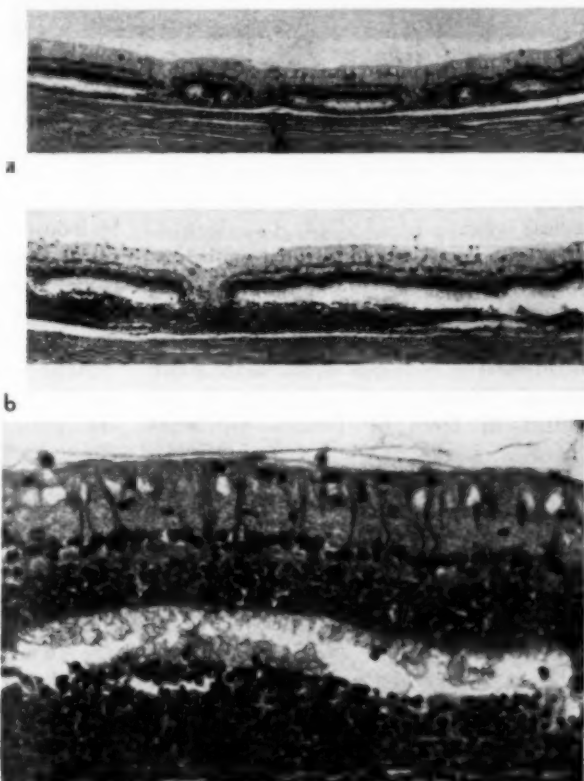


Fig. 6 (Noell). Retina of albino rabbit two weeks after intravenous administration of 5.5 cc. of a two-percent solution of sodium iodate. Hematoxylin-eosin (top and middle, $\times 90$; bottom, $\times 330$).

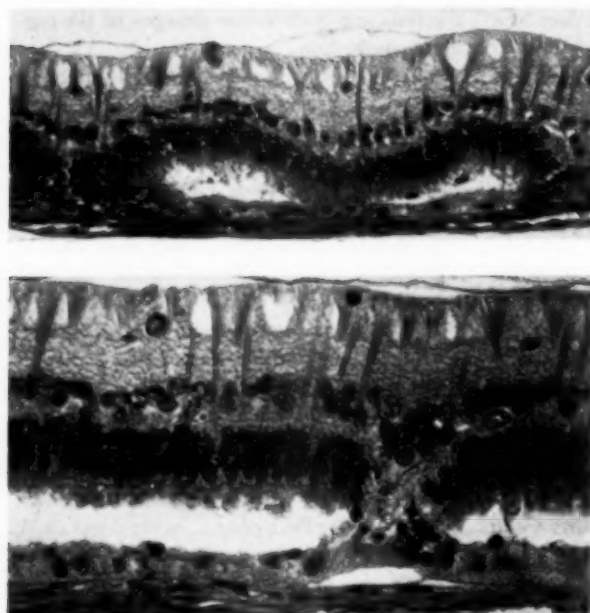


Fig. 7 (Noell). Retina of albino rabbits three weeks after iodate administration (same dose as in figure 6). (Top) Hematoxylin-eosin, $\times 300$. (Bottom). Hematoxylin-eosin, $\times 620$.

the pigment epithelium was altered everywhere three weeks after the injections, though over the greater part of the retina the inner segments had not disappeared and degeneration had not occurred in the outer nuclear layer.

In long stretches, the pigment epithelium was completely absent; in other areas, a few pyknotic cells had remained in contact with Bruch's membrane; and in still others, a broad band of homogenous substance which carried remnants of the pigment cells was located in front of Bruch's membrane (fig. 7).

The external limiting membrane was interrupted at spots and through such holes Müller cells and outer nuclei had moved and spread over the inner surface of Bruch's membrane (fig. 7), which conditioned the bizarre distortion (arcade formation) of the retina (fig. 6-a).

Disappearance of the outer nuclear layer was a rare event and when present it was restricted to small areas. In such areas the appearance of the retina was then about the

same as after administration of iodoacetate (fig. 8).

In their electrical properties, the eyes of albino rabbits which had been affected by iodate differed distinctly from those affected by iodoacetate. In the case of iodoacetate, a cornea-positive "steady" potential across the globe was generally maintained several weeks after the injections though no responses to illumination were evoked.

After iodate, on the other hand, weak responses to illumination were generally present, while the steady potential across the globe was almost invariably of reversed polarity. The same appearance was evident when recordings were made during acute experiments with injections of the drugs.

With iodoacetate, responses to illumination disappeared within several minutes while the steady potentials either remained unchanged or even increased. Iodate, when administered in higher doses than necessary for the production of permanent effects, only slightly changed the a- and b-wave of the electroretinogram in response to illumination within

the first hours after the injection; the steady potential of the eye, however, declined rapidly after the administration of the poison.

These differences were analyzed by correlating the histologic appearance of the retinas with their electrical properties.⁴ Using the sensitive reaction of the "steady" potentials to intravenous injection of small doses of azide, as an indicator, evidence was obtained that the "steady" potential of the eye depends on the integrity of the pigment epithelium.

Electrochemical processes seem to occur at the boundaries between retina and choroid, which are associated with the active transfer of ions between the retina and the retro-retinal tissue.

Very probably, therefore, the pigment epithelium and its associated structure, the glass membrane, serve an important function by participating in the maintenance of retinal homeostasis. Severe impairment of the pigment epithelium should alone, for this reason, be of consequence for the retina proper. The changes in the framework of the retina, as were observed both with iodoacetate and iodate, seem to point this out.

SUMMARY

1. Selective effects of sodium iodoacetate administered intravenously on the retina of rhesus monkey, cat, and albino rabbit are compared with retinitis pigmentosa. In all essential features the effects of iodoacetate

seemed to simulate the histologic changes described for retinitis pigmentosa.

The order in which iodoacetate affects the cell population of the retina is the same with which the disease progresses. The spatial distribution of cone, rod, and pigment cell impairment likewise appears to be the same, and the character of the histologic changes is very similar under both conditions.

It is concluded that the metabolic property which is responsible for the selective effectiveness of iodoacetate is distributed over retinal cell population in the same manner as that property which is affected by the genetic abnormality in cases of retinitis pigmentosa.

2. As indicated by the effects of iodoacetate, degeneration and proliferation of the pigment epithelium are not produced in reaction to visual cell degeneration. A direct effect of iodoacetate on the pigment cells is assumed to account for their reactions and their degeneration. Similarly it is suggested that the cause for the changes of the pigment cells in retinitis pigmentosa is the same which leads to degeneration of the neuro-epithelium.

3. Gliosis and destruction of the outer limiting membrane is closely associated with the degeneration of the pigment epithelium. Only weak reactions of glia elements are observed experimentally when the visual cells alone degenerate.

4. Sodium iodate intravenously adminis-

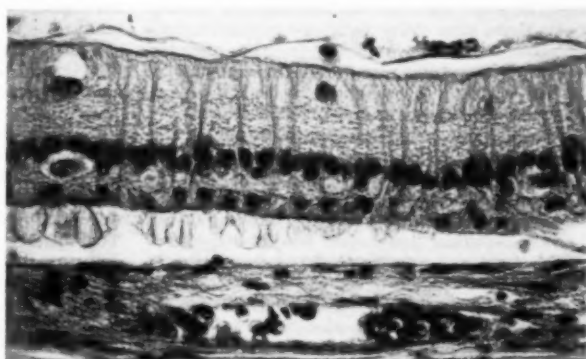


Fig. 8 (Noell). Retina, albino rabbit 25 days after iodate administration (same dose as in Figures 6 and 7). Heidenhain-phloxine, $\times 680$.

tered evokes retinal changes which differ from those of sodium iodoacetate, though both agents affect the outer layers of the retina. Degeneration of the pigment epithelium generally dominates the effect of iodate, which also leads to choroidal inflammation.

5. Iodoacetate and iodate produce different effects upon electrical phenomena recorded across the eye which are related to their different effectiveness upon the pigment epithelium.

School of Aviation Medicine.

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DISCUSSION

DR. LUDWIG VON SALLMANN (New York): I am much impressed by Dr. Noell's studies on the effect of iodoacetate on the retina of various animals. He knows, probably better than I, that since iodite intoxication was described by Riehm and Schimmel about 25 years ago, several investigators, Sorsby among them, have claimed that the fundus changes produced by iodate, iodite, and hypo-iodite resemble the changes in retinitis pigmentosa. This opinion has not been accepted by other investigators, however, because of the differences in the clinical characteristics of the fundus changes in the two conditions.

As shown by Kalt and others, intoxication with the iodate compounds, even in minimal doses, produced acute destruction of the pigment epithelium and neuro-epithelium. The marked scattering of the pigment epithelium leads to the fundus changes.

With respect to iodoacetate, I feel that it also is an acute intoxication and I would doubt whether the changes observed shortly after an intravenous injection of this metabolic poison could be said to

parallel the changes governing the pathogenesis of retinitis pigmentosa.

DR. NOELL: With regard to the question whether the pigment epithelium or the visual cells are more susceptible to iodate, it seems that both structures are directly affected, but the damage to the visual cells is probably enhanced by the degeneration of the pigment epithelium.

As to the other question concerning the comparison of the effects of an acute poison with retinitis pigmentosa, as a physiologist I certainly doubted that such comparison would be acceptable to you. What I wanted to point out is the identity in the distribution and character of the histologic changes. The metabolic property which, on the one side, determines the degenerative process in retinitis pigmentosa and which, on the other hand, determines the effectiveness of iodoacetate on the retina must, therefore, be distributed in the same manner. These

properties might be identical. That is the whole comparison I wanted to establish.

DR. ZACHARIAS DISCHE (New York): I would like first to ask what was the dose of iodoacetate which you applied.

DR. NOELL: In the cat, about 10 mg. per kg. For the rabbit, 18 to 20 mg. per kg., and for the monkey 30 or 35 mg. per kg.

DR. DISCHE: Those, of course, are large doses which in general would inhibit the whole metabolism of the cell. It is impossible to predict how much of it comes into the cells.

Also, I think there is one difficulty in your interpretation, namely, that the iodoacetate is an acute metabolic poison which stops the metabolic process. It stops it irreversibly, and in a very short time. It is difficult to see how chronic degeneration would result from such an effect. Furthermore, it is difficult to understand why the inhibitory process would be so selective, because the nerve cells of the retina are also extremely sensitive to iodoacetate.

On the contrary, one thing that might explain the effect would be an action on the thiol groups of the visual purple, which play a very great role in the visual process. The iodoacetate is a specific inhibiting poison for the thiol group, and in that case selectivity could be expected because the effectiveness of iodoacetate for the thiol group is something that may change very much with the general state of the proteins of the cell.

I wonder whether the thiol groups of the rhodopsin may not be involved rather than the glycolytic process.

DR. P. ROBB McDONALD (Philadelphia): May I ask a question on a point I didn't quite get clearly? Did Dr. Dische imply that the iodoacetate has its primary effect on rhodopsin, and that may cause secondary changes in the pigment epithelium?

DR. DISCHE: Yes, because the blockage of the thiol groups of rhodopsin interferes with the function of the visual purple mechanism. It is impossible to predict how much of the thiol groups are affected in the protein. It changes, depending upon the general state of the metabolism of the cell and depending upon the presence of certain other factors in the cell. The protein may be more or less receptive to the blockage. That may be the explanation.

DR. W. K. NOELL: Wald and Brown demonstrated that sulphydryl groups are involved in the binding of rhodopsin and that SH-reagents block rhodopsin regeneration. The implication of this finding with regard to the iodoacetate effect, I discussed in a paper just published (*Am. J. Ophth.*, 35:126 (May, Part 2) 1952). In Wald's experiments, iodoacetate was ineffective *in vitro*. It was

one of the SH-poisons not affecting the rhodopsin regeneration.

In our (*in vivo*) experiments the evidence also points against any direct effect of iodoacetate on visual purple mechanisms. Over the animal scale—frog, turtle, pigeon, cat, rabbit, monkey—the acute effects of iodoacetate on visual-cell function are not exactly the same. These effects differ depending upon the degree the various functions of the visual cells are either supported by respiratory (oxygen uptake) or glycolytic mechanisms.

We also measured the lactic-acid accumulation in the retina after removal of the eye from animals (rabbits) that were poisoned by iodoacetate five minutes previous to eye removal. Doses of iodoacetate, which transiently abolished visual cell function, reduced the lactic-acid accumulation to about 40 percent of its normal value over an eight minute period. The same doses were ineffective on the lactic-acid accumulation in brain and in skeletal muscle.

Moreover, compared with the *in vivo* effects of other enzyme poisons, we are working with very low concentrations of iodoacetate. Calculating the threshold dose of iodoacetate on the visual cells—the effect measured by electrical means—we have about the same threshold concentration as for the inhibition of lactic acid production.

There are many possible sites of action of iodoacetate. Since excessive glycolysis is the one property by which the retina differs from most other tissues, this property might also determine the selective effect of the poison. It is well known that the glycolysis of the retina exceeds even that of malignant tumors.

Your other point was, can one compare acute and chronic effects. Whether chronic or acute, specific cell processes are affected. In retinitis pigmentosa, a genetic abnormality affects somehow the metabolic mechanisms of the visual cells. One or more processes of the visual cell become disrupted and the maintenance of cell life is made impossible. The demonstration of an acute effect by experimental means is not an argument against the possibility that the same process is "chronically" affected in the disease. The genetic abnormality in retinitis pigmentosa becomes manifest with time; if iodoacetate affects the same process, which is the cell death determining the site of the reaction of the genetic abnormality, its effect has to become acutely manifest.

I may mention, however, that iodoacetate has also some unusual latent effects on the visual cells. For example, we observed one cat which had received a fairly low dose of iodoacetate. After a transient impairment of vision, the visual performances of both eyes were perfect.

During urethane anesthesia, we recorded the electroretinogram three weeks after the iodoacetate injection; it was not significantly altered. One eye was then removed; there were no histologic changes; no cell degeneration whatsoever was found.

Three days after the anesthesia, the pupil of the

remaining eye was found extremely wide, its reactions very weak; the animal was practically blind. We waited another three weeks and then removed the eye. Histologically, there now was widespread degeneration of the visual cells.

Somehow, urethane must have made manifest a latent change produced by the preceding iodoacetate administration. We have observed the same phenomenon occasionally with Dial anesthesia; I wonder, therefore, whether barbiturates have a similar adverse effect in cases of retinitis pigmen-

tosa. The effect of Dial in this respect was not strong; but with urethane we consistently observed the phenomenon with a varying degree of intensity. We assume that in these cases the transient inhibition of glycolysis by iodoacetate permanently changed the cell in a latent manner by affecting nuclear structures, and that urethane, which probably is a nuclear agent, magnified these changes and that it brought about cell death by indirectly affecting the same process which initially was the site of action of iodoacetate, namely glycolysis.

OBSERVATIONS ON THE EFFECT OF ADRENAL STEROIDS ON VACCINIA VIRUS*

I. THE EFFECT OF CORTISONE IN EXPERIMENTAL VACCINIA-VIRUS KERATOCONJUNCTIVITIS OF THE RABBIT

S. J. KIMURA, M.D., PHILLIPS THYGESON, M.D., AND
HILDEGARD ODENHEIMER GELLER, M.A.

San Francisco, California

Many inflammatory eye diseases have been treated successfully with cortisone. Its most dramatic effect has been exerted on such allergic inflammations as vernal catarrh, on the eye manifestations of the so-called collagen diseases, and on those bacterial infections, for example, nongranulomatous uveitis and phlyctenulosis, in which bacterial allergy is believed to be largely responsible for the inflammatory signs.

No evidence has been advanced to suggest that the hormone has any direct bacteriostatic or bactericidal effect. On the contrary there are indications that it may promote the dissemination of bacteria, for example, in tuberculosis,¹ of fungi, for example, in coccidioidomycosis,² and especially of viruses.

This disseminating effect on viruses was noted in connection with poliomyelitis virus by Schwartzman,³ and in connection with influenza virus and mumps virus by Kilbourne

and Horsfall⁴ who increased the growth of both viruses on the chorioallantoic membrane of eggs by injecting the eggs with cortisone. The same investigators⁵ later showed that adult mice, ordinarily insusceptible to Cox-sackie virus infection, could be lethally infected if cortisone were administered prior to the virus inoculation.

Cortisone has been found to have this same disseminating effect on experimental herpes-simplex virus keratitis of the rabbit by three groups of investigators working independently.

Thygeson, Geller, and Schwartz⁶ noted that the infections produced by three different strains of herpes virus were unimproved by topical instillations, subconjunctival injections, or intramuscular injections of cortisone, and that the infections were usually more severe in the cortisone-treated animals than in the controls.

Hallett and co-workers⁷ found that rabbits treated with cortisone in the form of drops, ointment, or subconjunctival injection generally showed more severe infections than control rabbits.

* From the Francis I. Proctor Foundation for Research in Ophthalmology and the Department of Ophthalmology, University of California School of Medicine. This work was supported in part by a grant from The Gustavus and Louise Pfeiffer Research Foundation.

In a more extensive study, Ormsby, Dempster, and van Rooyen⁸ noted that in rabbits receiving large intramuscular doses of cortisone the acute phase of the herpetic infection was prolonged and the onset of healing delayed. They also noted, however, that the cortisone appeared to have a tendency to restrain corneal vascularization.

In an effort to examine further the apparently profound effect exerted by cortisone on the resistance of animal tissues to viral infections, a study of its effect on experimental vaccinia virus keratitis of the rabbit was undertaken. This disease seemed peculiarly suited to this purpose by reason of its remarkably uniform clinical picture and course.

At the time of writing the only related observations on this virus known to have been reported are those of Kligman, Baldridge, Rebell, and Pillsbury,⁹ and of Rose, Holden, Blunt, and Ragan.¹⁰ Kligman and his co-workers noted that the course of vaccinia infection in the guinea pig after intradermal inoculation was adversely affected by treatment with intramuscular injections of cortisone, and Rose and his co-workers found an increased incidence of fatal encephalitis in cortisone-treated rabbits that had received intradermal injections of the virus.

MATERIALS AND METHODS

Available for this study were white rabbits of a strain which had proved to be uniformly susceptible to corneal inoculation with vaccinia virus. The virus used was the C.V.I. strain harvested on the chorioallantoic membrane of the developing chick embryo.

The cortisone was the saline suspension of cortone acetate (Merck & Co., Inc.), undiluted for intramuscular and subconjunctival use and diluted with saline 1:3 for local instillation. The cortisone ointment was the 1.5-percent ophthalmic ointment of cortone acetate (Merck & Co., Inc.). Aqueous Vehicle No. 1 (Merck & Co., Inc.), the suspending vehicle for cortone acetate, was

used in the control eyes of the rabbits receiving the 1:3 dilution of cortone acetate in one eye. The base for the 1.5-percent ophthalmic ointment of cortone acetate, which contains 75-percent petrolatum and 25-percent liquid petrolatum, was used in the control eyes of rabbits receiving cortisone ointment in one eye.

The rabbit corneas were inoculated with six-mm. trephine. The tip of the trephine was wet with the virus suspension (10^{-1} dilution), and a half-turn was made with the trephine against the anesthetized cornea. By this method a rough standardization of the amount of virus inoculum was achieved.

EXPERIMENTAL VACCINIA VIRUS KERATOCONJUNCTIVITIS

The experimental disease develops after an incubation period of from three to five days and resembles in appearance and clinical course the keratoconjunctivitis produced by herpes simplex virus. The keratitis appears in the form of superficial corneal infiltrates followed by vascularization; the conjunctivitis is characterized by an intense cellular infiltration of the entire conjunctiva with exudation.

Early in the course of the keratitis there are even dendritic figures identical in appearance with those occurring in typical herpes-simplex keratitis; these are more likely to be seen in the early stages of the experimental disease and may not be noticeable when massive inoculations have been made. The disease runs a three- to four-week course and heals spontaneously.

EXPERIMENTAL RESULTS

EXPERIMENT 1

The effect of cortisone administered intramuscularly after the onset of vaccinia virus keratoconjunctivitis:

Both eyes of 10 rabbits were inoculated with vaccinia virus. After the onset of the keratoconjunctivitis, six rabbits were injected with 20 mg. cortone acetate intra-

muscularly daily for 11 days. Four rabbits were reserved as controls.

In three of the six treated rabbits the ocular disease was significantly more severe than it was in the control rabbits; in the other three it was of the same intensity as in the untreated animals.

EXPERIMENT 2

The effect of cortisone suspension instilled into the conjunctival sac before the onset of the keratoconjunctivitis:

In six rabbits the right eye was treated with one drop of diluted (1:3) cortone acetate at one-hour intervals during the day. The drops were started one day after the corneas had been inoculated with vaccinia virus. The fellow eyes received one drop of suspending Vehicle No. 1, also at one-hour intervals during the day. Two control rabbits were inoculated with virus but the eyes were left untreated.

In three of the six treated animals the keratoconjunctivitis was more severe in the treated than in the untreated eyes; of the remaining three treated rabbits, one showed a less severe ocular disease in the treated eye and two showed equally severe disease in the treated and untreated eyes.

EXPERIMENT 3

The effect of cortisone injected subconjunctivally before the onset of the keratoconjunctivitis:

Both eyes of six rabbits were inoculated with vaccinia virus and the next day the right eye of each rabbit was injected subconjunctivally with 2.5 mg. cortone acetate. The left eyes were left untreated. The subconjunctival injections of the right eyes were repeated every other day for a total of six injections. Three control rabbits were inoculated with virus but were left untreated.

The results of this experiment were equivocal. In only one of the treated eyes was the keratoconjunctivitis more severe than it was in the control eyes. In the others there were no significant differences between

the treated and the untreated disease and the final scarring and vascularization seemed to be much the same in the treated as in the control eyes.

EXPERIMENT 4

The effect of cortisone injected intramuscularly one day prior to inoculation of the cornea with vaccinia virus:

Each of six rabbits was given 20 mg. cortone acetate intramuscularly 24 hours prior to inoculation of its cornea with the virus and on eight successive days thereafter. Two control rabbits were inoculated with virus but were left untreated.

There were no significant differences in the ocular disease in the treated and untreated rabbits, but three of the treated animals eventually died of encephalitis.

EXPERIMENT 5

The effect of cortisone ointment instilled into the eye before the onset of the keratoconjunctivitis:

The ophthalmic ointment (1.5 percent) of cortone acetate was instilled into the right eye of each of six rabbits three times daily for 11 days; the treatment was started one day after the inoculation with virus; ointment base was instilled into each left eye.

Although four of the six cortisone-treated eyes showed a more severe keratoconjunctivitis than the untreated eyes, the differences were slight and, after healing, the corneal scars were about the same in the treated as in the control eyes.

COMMENT

In these experiments on 30 rabbits cortisone administered by various routes failed to influence favorably the course of experimental vaccinal keratitis. Contrary to the observations of Ormsby, Dempster, and van Rooyen⁸ on herpetic keratoconjunctivitis, it also failed to restrain corneal vascularization. As was found to be the case in experimental herpetic keratoconjunctivitis by Thygeson, Geller, and Schwartz,⁶ and by Ormsby and

others,⁸ cortisone administered intramuscularly in the vaccinia-infected rabbits seemed to favor dissemination of the virus. Thus in three of six treated rabbits in Experiment 1 the disease was significantly more severe than in untreated control rabbits, and in Experiment 4, in which none of the control animals developed encephalitis, three of the six treated animals succumbed to this complication.

In general, therefore, cortisone had an adverse effect on experimental infections with vaccinia virus just as it has been shown to have on such other virus infections as poliomyelitis, herpes simplex, Coxsackie infection, and influenza.

SUMMARY AND CONCLUSIONS

1. The effect of cortisone therapy on experimental vaccinia virus keratoconjunctivitis was tested in a series of five experiments on 30 rabbits.
2. Cortisone administered prior to the

onset of the keratoconjunctivitis by intramuscular injection, subconjunctival injection, and drop and ointment instillation failed to exert a protective action or to influence favorably the course of the disease.

3. In a significant number of rabbits treated variously with cortisone prior to the onset of the keratoconjunctivitis the disease was more severe than in the untreated controls.

4. When the cortisone was administered intramuscularly prior to inoculation with the virus, the ocular disease developed with equal severity in the treated and untreated eyes, but three of the cortisone-pretreated rabbits died with symptoms of encephalitis; none of the control rabbits developed encephalitis.

5. In a significant number of instances in this experimental series cortisone apparently increased the dissemination of vaccinia virus.

*University of California
Medical Center (22).*

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DISCUSSION

DR. DAVID COGAN (Boston): If I understood you correctly, I think this has profound practical ap-

plications. Dr. Kimura did not say anything about other viruses, but I would infer that the vaccinia

virus is being used just as a test agent, and that what applies to the cortisone effect on vaccinia virus is true of other viruses as well.

If so, that is a very practical matter for us, is it not? Is it your belief, Dr. Kimura, that this applies to viruses in general?

DR. KIMURA: Dr. Thygeson has previously reported on the effects of cortisone on the herpes simplex virus and, as I recall, there were indications that the use of cortisone certainly did not help the herpes simplex keratitis.

As I said, this is just part of a general program in which we have been studying the effect on various viral infections not only of cortisone but of other adrenal steroid hormones.

DR. A. E. BRALEY (Iowa City, Iowa): We have not conducted our experiments with cortisone on viruses along the same lines, but we have an indication that cortisone has no good effect on virus infections.

I don't believe we can actually say that it increases the susceptibility of the body to virus infections. Certainly in certain clinical virus infections, such as epidemic keratoconjunctivitis, when cortisone is used, as it is in herpes simplex, there is not a good effect on the clinical disease or the spread of the virus. In the spread of the epidemic keratoconjunctivitis virus during the active phase there is probably an increase in the number of corneal opacities that are present after the use of cortisone. However, after the corneal opacities develop and the virus disease has run its course, cortisone may have a beneficial effect.

DR. H. E. THORPE (Pittsburgh): I should like to mention my experience with several cases of dendritic keratitis which were treated with topical application or with subconjunctival injection of cortisone acetate. None of the cases in which topical cortisone was applied showed any improvement during the use of this drug. Two cases in which cortisone was injected subconjunctivally in dosage of 10 mg. were definitely and markedly aggravated within 24 to 36 hours.

When, however, these cases were subsequently treated with intramuscular or intravenous injections of corticotropin (ACTH), there was a marked regression of the inflammatory process.

Human dendritic keratitis ascribed to virus disease is often complicated by severe inflammation which may be due to other factors. The few cases which have come to our attention have in most instances responded favorably to systemic ACTH therapy and unfavorably to local cortisone treatment. It is likely that this is due to the fact that corticotropin or ACTH stimulates the production of a broad spectrum of corticoid substances.

DR. M. A. LAST (New York): There appears to be no question that, in experimental animals, cortisone does seem to have a deleterious effect in infections; but one of the interesting things is that in virus infections of other parts of the body, such as poliomyelitis, as described by Schwartzman, ACTH does not have that effect but cortisone does.

Secondly, while the experimental effects of cortisone have not been at all good, there have been reports in the treatment of other virus infections clinically (not in the eye) wherein cortisone did not have a bad effect. I am not talking about local treatment—I mean systemic therapy.

CORTISONE IN EXPERIMENTAL HOMOLOGOUS KERATOPLASTY IN THE RABBIT*

GAYLORD W. OJERS, M.D., JULES M. YASUNA, M.D., AND
HAROLD G. SCHEIE, M.D.
Philadelphia, Pennsylvania

The postoperative course following keratoplasty in human eyes is characteristically smooth for the first two weeks and the graft remains clear. However, at any time from the end of the second to the fifth postoperative week signs of varying degrees of iridocyclitis appear and there is a tendency of the graft to become hazy and vascularized. This

is thought by some¹⁻⁷ to be due to an intolerance on the part of the eye to the foreign protein of the donor button, probably similar in nature to the reaction which occurs in homologous skin grafts.

Homologous skin grafts also do well for the first two or three weeks but then undergo necrosis or exfoliation. The analogy between the two types of grafts is suggested not only because the time of reaction is similar in each, but also because corneal grafts placed into heavily scarred and vascularized corneas

*From the Department of Ophthalmology, Hospital of the University of Pennsylvania, Medical School of the University of Pennsylvania, and the Children's Hospital of Philadelphia.

undergo more marked reaction and are more likely to become opaque than when placed in lightly scarred, avascular ones. A vascularized, scarred cornea more nearly resembles the subcutaneous recipient bed of the skin transplant. The avascular, lightly scarred cornea contains few cells and no blood vessels and is probably not capable of giving rise to severe foreign protein reactions.

The exact mechanism underlying the delayed reaction to the homologous tissue grafts is not known. Some of the reasons given are: (1) Athrepsia (a lack of nutrient in the host), (2) natural immunity, (3) a lack of stroma and vascular supply, (4) a possible local cellular reaction leading to the production of substances causing incompatibilities between the host and transplant, (5) or a possible production of an actively acquired immunity on the part of the host to the foreign protein.⁸

The latter theory of an actively acquired immunity receives support from the work of Medawar,⁹ who has demonstrated in rabbits that a second crop of skin transplants from the same donor will disintegrate at a much faster rate than the first. He has also stressed the fact that the larger the graft (the greater the dose of the antigen), the more rapid is the disintegration of the graft.¹⁰

In such experiments, antibodies to the skin protein cannot be found, a situation similar to that seen in tuberculin hypersensitivity, wherein there is also an absence of demonstrable antibodies in the serum to the tuberculo-protein.

In discussing the anomalous situation of the survival of the corneal grafts as contrasted to skin grafts, Medawar¹¹ points out that even skin grafts when transplanted into the anterior chambers of specifically immunized rabbits will not be destroyed unless vascularization of the graft takes place.

Since the cornea is avascular, the corneal button is not likely to succumb to an immune reaction even if it could initiate it. The fact that corneal grafts do poorly when placed

in scarred, vascularized corneas adds clinical support to this explanation.

Maumenee¹ has performed a very interesting set of experiments wherein keratoplasty in rabbit eyes resulted in clear transplants if the ocular reaction during the first two weeks was mild, the pannus not marked, and the graft clear or only slightly hazy. This is in marked contrast to the course of human eyes following keratoplasty, where grafts not infrequently appear clear during the first two postoperative weeks, only to become cloudy and the eye irritated a short time later.

Maumenee felt that possible explanations for this variance in postoperative course might lie in the fact that rabbit corneas are not as susceptible to donor recipient sensitization as is man and the corneal buttons did not release sufficient antigen to give rise to a sensitivity reaction.

At any rate, it is most interesting that Maumenee was able to produce clouding in previously clear corneal grafts two to four weeks after transplanting skin from the corneal donor animal to the corneal recipient rabbit. This, of course, corresponds to the time sequence of reaction seen in the human eye after keratoplasty. Systemic cortisone given to a small series of such animals resulted in some instances in the clearing of the graft.

The delayed response of the human eye following keratoplasty offers some support to the sensitization theory. Scheie^{1,3} has found clinically in 10 cases that cortisone was at least partially effective in blocking the secondary reaction of the eye and clouding of the graft. Others^{12, 13} have mentioned its use in keratoplasty. It, therefore, seemed worthwhile to investigate the effect of cortisone on the postoperative course of eyes following keratoplasty.

METHODS

Male albino rabbits were used. The animals undergoing keratoplasty operations were divided into four groups. Homologous

keratoplasties were performed on the animals in the first three groups. The fourth group consisted of rabbits with autologous keratoplasties. The first and last groups received no cortisone. Cortisone acetate was given systemically to the second group from the day of surgery and continued for 20 postoperative days. The animals of the third group were given systemic cortisone from the seventh to the 27th postoperative days.

Animal preparation and basic procedures closely resembled that described by Katzin.¹⁴ The rabbits were given intravenous pentobarbital sodium in basal anesthetic doses (25 mg./kg.) combined with 25 units of heparin to prevent the troublesome coagulation of secondary aqueous. Each animal was immobilized in a small animal holder and the eye was prepared by the instillation of drops of pontocaine (1.0 percent), pilocarpine (1.0 percent), and physostigmine (0.5 percent). The eye was then immobilized with fixation sutures placed through the recti muscles.

After outlining the area of the transplant with a 4.5-mm. trephine, the cornea was stained with fluorescein, and 6-0 black silk, criss-cross sutures were placed in the cornea. Following the removal of the donor graft from the eye of a freshly killed rabbit, the button from the recipient eye was removed by a combination of trephination and scissor dissection. Just prior to placing the transplant and tying the sutures, several drops of neosynephrine (10 percent) and atropine sulphate (1.0 percent) were instilled directly into the opened eye.

In the autologous keratoplasties, the technique was the same except that the button was removed from the living rabbit and then replaced in the same eye.

Postoperatively, all animals received daily intramuscular injections of procaine penicillin (50,000 units) and dihydrostreptomycin (0.025 gm./kg.) for five days. Atropine sulphate ointment (1.0 percent) was instilled into the cul-de-sac of the operated eye until

all signs of irritation had ceased. About one half of the animals were given 6.0 mg. of cortisone acetate per kg. intramuscularly, either from the day of operation or starting on the seventh postoperative day. This was continued for 20 days. The transplanted eyes were examined at two- to three-day intervals for iridocyclitis, graft clarity, and corneal vascularization.

The iritis was graded by the amount of iris vessel dilatation and visibility of iris detail. The grading ranged from no change (zero) to marked vascular engorgement with iris hemorrhages and obliteration of iris details (Grade 3).

Graft clarity was judged by the amount of iris detail visible through the corneal button and the observable graft haze. A zero grade represented no corneal haze; a just discernible haze was Grade 1; grafts which showed well-marked haze, but with iris detail visible, were graded as Grade 2; Grade 3 included those grafts so opaque that no iris details could be distinguished. For purposes of final classification Grades 0 and 1 were classed as clear. Grades 2 and 3 were classed as opaque.

Corneal vascularization was judged by the size of the invading vessels, the numbers of vessels or density, and distance of the corneal invasion in millimeters.

OBSERVATIONS

HOMOLOGOUS KERATOPLASTY IN ANIMALS NOT TREATED WITH CORTISONE

By the second or third day (the time of the first postoperative observation) most of the grafts showed a Grade-2 or Grade-3 haze. In most of those corneas which eventually cleared, a definite decrease in corneal haze was observed by the 10th to 14th postoperative day. Maximum clarity was reached as early as the second and as late as the fourth week. None cleared after this.

Circumcorneal vascular dilatation was present from the first, and corneal invasion began about the fourth or fifth postoperative

day. At this time, the vessels were densely packed and small. Some of the vessels increased in size and length to reach the graft by the 14th day. It is interesting to note that the vessels reached the graft at the approximate time that the graft began to clear.

No general statement can be made with regard to the ultimate fate of the vessels. In some instances, the vessels became smaller and lost their blood content. In others, the vessels were stationary in size and blood content. If vessels had ever been in the cornea, at least ghost vessels could always be detected on subsequent examination with magnification and intense illumination.

The iritis was maximal during the first week or 10 days and subsided about the 16th day.

The period of greatest reaction as judged by the most intense combination of iritis, vascularization, and graft density occurred somewhere between the seventh and 16th postoperative days.

HOMOLOGOUS KERATOPLASTY IN CORTISONE-TREATED ANIMALS

The period of greatest reaction in animals treated with cortisone from the time of surgery was from the second to fifth day. Not only was the duration of the reaction decreased, but all component phases of the reaction were minimized. The intensity of the reactions seen from the seventh to 16th postoperative days in the control animals was never approximated in the cortisone-treated animals. The cortisone did not hasten the height of reaction; rather it appeared to cut

TABLE 1

THE EFFECT OF CORTISONE ON DAY OF GREATEST REACTION FOLLOWING CORNEAL TRANSPLANTATION

	Days of Greatest Reaction	Average
Control with atropine	7-16	12
Cortisone with atropine from day of surgery	2-5	4
Cortisone and atropine from 7th postoperative day	6-9	8

TABLE 2

THE EFFECT OF CORTISONE ON THE DURATION OF IRITIS AFTER CORNEAL TRANSPLANTATION

	Duration of Iritis (days)	Number of Eyes
Control with atropine	16.5	34
Cortisone from day of surgery	5.5	18
Cortisone from 7th postoperative day	8.0*	9

* Lasted two days after start of cortisone.

the reaction short before it became full blown.

The period of greatest reaction when cortisone was started on the seventh postoperative day was seen from the sixth to ninth day, which again shows the marked effect of cortisone (table 1).

Duration of iritis. In the 34 homologous control eyes, the average duration of the iridocyclitis was 16 days. When cortisone was started on the day of operation, the average duration of the iridocyclitis in 18 eyes was 5.5 days, which is approximately one third of the figure for the controls.

Cortisone given on the seventh postoperative day resulted in a cessation of the iritis on the eighth postoperative day in all nine eyes (table 2).

Corneal vascularization. Of the 34 homologous control eyes, 31 showed vascularization of varying degrees.

Not one of the 18 eyes of rabbits receiving cortisone from the day of surgery developed corneal vascularization.

All nine of the eyes of the rabbits receiving cortisone from the seventh postoperative day developed some degree of vascularization. However, the size of the blood column in this group decreased soon after the starting of the cortisone. While the same phenomena eventually occurred in the control eyes, this tendency was more marked and occurred sooner in the former group.

Graft clarity. Of the 34 homologous control eyes, 17 or 50 percent were eventually graded as clear.

TABLE 3

THE EFFECT OF CORTISONE ON GRAFT CLARITY

Percentage of Cortisone Eyes Treated from Day of Operation Remaining Clear	Percentage of Cortisone Eyes Treated from 7th Postoperative Day Remaining Clear	Percentage of Control Eyes Remaining Clear
90% (16 of 18 Eyes)	80% (7 of 9 Eyes)	50% (17 of 34 Eyes)

When cortisone was given from the day of surgery 16 of the 18 grafts or 90 percent were eventually graded as clear.

Clear grafts resulted in seven of the nine (80 percent) eyes in rabbits receiving cortisone from the seventh postoperative day (table 3).

AUTOLOGOUS KERATOPLASTY IN ANIMALS NOT TREATED WITH CORTISONE

The 10 rabbit eyes in this series ran a course very similar to the control eyes with homologous keratoplasties. The autologous grafts were hazy at the time of the first postoperative dressing (second or third postoperative day). The average duration of the iritis was 18 days.

Corneal vascularization began about the fourth or fifth postoperative day. Three of these 10 eyes showed no vascularization as compared to three of the 34 control eyes with homologous transplants.

Although the higher percentage of non-vascularization in the autologous keratoplasties may be significant, it does not seem possible to draw such a conclusion from so small a number of rabbits. Five of the grafts in the autologous series were graded as clear at the end of the third postoperative week. While this percentage is identical to that found in the homologous controls, it is unfortunate that the autologous grafts were followed for only three weeks, as it was found that a few of the homologous controls followed for a longer time reached maximal clarity between the third and fourth postoperative week.

DISCUSSION

The postoperative course following keratoplasty in the untreated rabbit eye was similar to that described by Maumenee.⁴ The reaction as judged by the amount of iridocyclitis, corneal vascularization, and haziness of the graft started during the first three days and reached its peak during the second week. Grafts which were relatively clear by the 16th day almost invariably remained so. Further reaction did not then occur, as the process was apparently self-limited.

There was little difference in the postoperative course of the control eyes with homologous keratoplasty as contrasted to the eyes with autologous keratoplasty. Although three of the 10 eyes with autologous grafts showed no vascularization as compared to three of the 34 control homologous keratoplasties, the series are not complete in numbers and the figures can therefore only be considered as suggestive of less postoperative irritation in the eyes with autologous grafts.

It would appear that the stormy postoperative course of the rabbit eye following keratoplasty was chiefly due to postoperative irritation rather than foreign tissue intolerance. This might be interpreted as offering some support to Castroviejo's^{15, 16} theory that the stormy postoperative course in humans is due to factors other than a reaction to homologous tissue.

Whatever the cause of the stormy postoperative course in rabbit eyes with keratoplasties, the modifying effect of systemic cortisone on the reaction is notable.

The inhibition of corneal neovascularization in the animals treated with systemic cortisone from the day of surgery is striking. None of these animals developed corneal vascularization. There is evidence that cortisone inhibits corneal vascularization following experimental corneal injury induced by the application of heat,^{17, 18} alloxan,¹⁹ or alkali.²⁰ Although all workers²¹ have not been able to confirm this in alkali burns, this may

be due to the fact that cortisone is not equally effective in overcoming varying intensities of alkali injury. Furthermore, the effect of alkali may be more persistent and result in greater tissue damage than either heat or alloxan.

Inhibition of vascularization by cortisone in other parts of the body has been reported. Blunt²² and others attribute the delay in healing of fractured rat femurs in cortisone-treated animals to an inhibition of new blood vessels in the reparative process. Billingham²³ and co-workers report a delay in the vascularization of skin autografts in cortisone-treated rabbits.

Because neovascularization of the cornea is inhibited or lessened by cortisone, Gordon¹² and others, and Hartmann¹³ and others have suggested its use in transplant surgery. Favorable results on neovascularization in human transplants have been reported by Scheie,¹ Woods,²⁴ and Duke-Elder.²⁵

The salutary effect of cortisone on acute iritis has been well documented, and it is therefore not surprising that this drug markedly cut down the degree and duration of the postoperative iritis in our experimental animals. This may be one of the contributing factors which resulted in a larger number of clear grafts in the treated animals.

In our control rabbits only 50 percent of the eyes with keratoplasties were eventually classified as having clear grafts. Since this figure corresponds to the results obtained by

Maumenee,⁴ it seems quite significant that the corneal grafts were clear in 80 to 90 percent of the cortisone-treated animals.

Newell²⁶ and co-workers gave subconjunctival injections of cortisone in a series of rabbit eyes with keratoplasties. After the third and through the 14th postoperative days (at which time their animals were killed), they felt that there was more bulging of the graft and that the graft and surrounding cornea were less clear than in their control animals. We are unable to explain the variance between the findings of these authors and ours.

CONCLUSIONS

1. It would appear that the ocular reaction following keratoplasty in rabbit eyes is consequent to the operative trauma rather than allergy to homologous tissue.

2. Cortisone decreases the duration and severity of the ocular reaction to keratoplasty in rabbit eyes.

3. Corneal neovascularization appeared to be inhibited when systemic cortisone was started on the day of surgery.

4. Postoperative iridocyclitis was reduced in amount and duration by systemic cortisone.

5. The percentage of clear corneal grafts was increased in those rabbits receiving cortisone postoperatively.

313 South 17th Street (3).

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DISCUSSION

DR. LUDWIG VON SALLMANN (New York): Have you noticed any effect on wound healing secondary to the administration of cortisone?

DR. OJERS: Not in the corneal transplants, but we have done some experiments, which we intend to report later, with linear incisions. At various time intervals, the partially healed incisions were ruptured by increasing the intraocular pressure. Histologic sections would seem to indicate that there is a decrease in the fibroblastic repair after the sixth day, but as far as tensile strength is concerned we have not demonstrated any change.

DR. FRANK W. NEWELL (Chicago): Quantitatively there is a difference between the systemic administration of cortisone and the local administration of cortisone following keratoplasty. Histologically, in all of these eyes there is no delay in wound healing in the first four or five days because mesenchyme proliferation is not significant in wound

healing during that period. Epithelial proliferation, which is not affected materially by cortisone, proceeds normally.

Unless one wishes to propose something which I do not think has been proposed previously, namely, that there is a differential effect of cortisone upon neovascularization and fibrous tissue regeneration, it is going to be difficult to accept fully the thesis that cortisone depresses new blood vessel formation without also depressing fibrous tissue regeneration, since they are both mesenchymal tissues.

DR. OJERS: I don't believe I said it did not depress the fibroplastic tissue. I believe I said our pathologist thought he could prove that it did, but that in the clinical part or the bursting experiments it did not seem as though the amount of depression was significant, although I would like to point out that we had a tremendous scatter in the bursting points of these various eyes.

THE NUTRITIONAL SUPPLY OF CORNEAL REGIONS IN EXPERIMENTAL ANIMALS*

II. THE PROBLEM OF CORNEAL TRANSPARENCY AND THE TONICITY OF TEARS

ALBERT M. POTTS, M.D.

Cleveland, Ohio

(With the technical assistance of Mildred Orchen, B.A.)

All of the optical media of the eye have in common the necessity of maintaining transparency for preservation of function. The cornea presents a particularly difficult problem in that it is a highly cellular structure with substantial metabolic activity and nutritional requirements, but because of the transparency requirement it must remain avascular. Moreover, the maintenance of transparency is due entirely to maintenance of the same refractive index in intra- and extracellular fluid.

In a living tissue, this means maintenance of a specific solute concentration and, in the cornea, it has been demonstrated that the tissue is in a state of partial dehydration; increase or extreme decrease in water content causes marked loss of transparency. The homeostatic mechanisms involved here are of great practical interest to the ophthalmologist. A certain amount of experimental work and much speculation has been devoted to this problem of corneal transparency.

Leber who first emphasized the connection between deturgescence and transparency believed the epithelium and endothelium to be completely impermeable to salts and water.¹ Later Grüber² showed that the limbal vascular plexus was the source of corneal water and salts by free flow. Grüber suggested two possible patterns of flow: one in re-entrant arcs, from limbus to center to limbus again; or a second with entry at the limbus and exit into the aqueous centrally.

Fischer in a series of papers³ reported selective permeability differences between epithelium and endothelium. The extensive work of Cogan and co-workers⁴ has led to the postulation of a very specific theory of corneal fluid flow which runs briefly as follows:

The chief source for corneal nutrition is the limbal vascular plexus; fluid and salts enter freely here. The corneal epithelium and endothelium are virtually impermeable to salts but not to water. Furthermore, according to these workers, both tears and aqueous are moderately hypertonic with respect to plasma so that water is removed from the cornea osmotically in both directions leaving the salt to diffuse back via the limbus. According to this theory the work of keeping the cornea dehydrated is performed by the lacrimal gland in secreting hypertonic tears and by the ciliary body in secreting hypertonic aqueous.

Davson⁵ has correctly pointed out that if this mechanism actually did obtain, the result would be an increase of salt concentration within the cornea to the point where the postulated mechanism would soon stop. This objection has not been satisfactorily answered by Kinsey's postulate of a small osmotic gradient causing a steady-state with little actual water transfer.⁶

The demonstration in this laboratory⁷ of the rapid corneal entry of intravenously injected inorganic ions (30 to 50 percent of serum level in 15 minutes) is hardly compatible with no fluid flow. Thus the present state of the problem of corneal transparency is an unsatisfactory one, and is subject to revision.

It is to be noted that part of the Cogan-

*From the Laboratory for Research in Ophthalmology, Western Reserve University, and the Ophthalmologic Service, Department of Surgery, University Hospitals of Cleveland. Supported by a grant from the National Institute of Neurological Diseases and Blindness, U. S. Public Health Service.

Kinsey theory is based on the assumption of tears hypertonic to the plasma and a cornea impermeable to inorganic ions. These two assumptions were tested in the experiments to be described herein. It should be further noted that an accurate estimate of the tonicity of tears is a desirable and unusually difficult figure to come by. Such an estimate is of interest for preparation of local ocular medications in addition to its theoretical utility. However, direct measurement of the thin watery film which covers the normal cornea is impossible by our present methods.

Measurement of the osmotic pressure of stimulated tears⁸ or of tears collected from the duct of the lacrimal gland before evaporation is certain to yield lower concentrations than would be given after normal evaporation has taken place from the corneal film. Most of the results on the unevaporated preparations were in the neighborhood of 0.9 percent NaCl equivalent. In the face of these difficulties an indirect approach may be necessary to give useful results.

Such an indirect approach is the application of solutions of graded tonicity to the anterior corneal surface of an experimental animal and measuring the amount of penetration of a specific inorganic ion in a given time period. At any tonicity other than the optimum there should be epithelial damage and increased permeability.⁹

This indirect approach to the tonicity of tears should be a direct approach to the best tolerated osmotic concentration for local medications. Such an approach was also used by Massart¹⁰ who measured observer sensation in response to solutions of varying tonicity dropped on the cornea. His findings indicated that tears were equivalent osmotically to 1.35-percent sodium chloride.

This same type of experiment furnishes information on the outside—in permeability of the corneal epithelium. To get information on the inside-out permeability of both epithelium and endothelium one may inject small volumes of solution into the stroma via the limbus without damaging either endo-

thelium or epithelium and measure penetration both into the aqueous and into an eye bath of artificial tears. Finally, penetration from aqueous to cornea through the endothelium may be measured after careful injection of the anterior chamber through the filtration angle. Because of ease of analysis and ability to determine physiologic amounts of inorganic salts even when small volumes were introduced, all experiments were done with radioactively labeled inorganic salts.*

The results discussed in detail herein indicate a markedly higher osmotic optimum for fluids in contact with the anterior corneal surface than generally reported in the literature, and an unsuspectedly high permeability of the endothelium to ions diffusing from the corneal stroma to the aqueous.

METHODS

A. PERMEABILITY OF ANTERIOR CORNEAL SURFACE IN OUTSIDE-IN DIRECTION

These and all subsequent experiments were done on the eyes of healthy adult rabbits under phenobarbital-pentobarbital anesthesia. Test solutions were applied to the anterior corneal surface by means of a glass-cup applicator similar to that described by Cogan and Hirsch¹¹ and held in place by a minimum amount of suction. In our hands this amounted to 10 mm. Hg, a level which, in agreement with the above authors, is far too little to cause trauma (see protein experiments to be described).

It was found that a 2.0 ml. pyrex centrifuge tube made an admirable applicator when the tapered end was opened and attached to the source of vacuum. Usually six of each dozen tubes had lips which were shaped well enough to require no further modification. The area of solution in contact with the cornea was 3.14 cm.², that is, a circle 10 mm. in diameter. A modification found useful later was the addition of a side-arm for removal of the applied solution (fig. 1).

* Obtained from Oak Ridge National Laboratory, Oak Ridge, Tennessee.

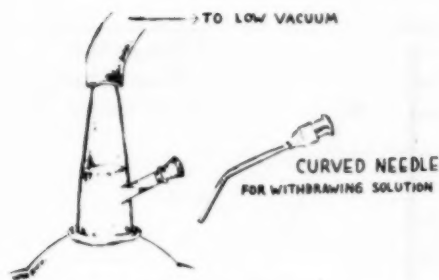


Fig. 1 (Potts). Improved applicator for studies of permeability of corneal epithelium.

The solution to be tested was injected through the rubber tube and into the cup. The volume injected was 2.0 ml. of a solution containing M/150 phosphate buffer at pH 7.3, the salt to be tested was in osmolar concentration equivalent to 700 mg. NaCl/100 cc. and the solution made up to the specified osmotic strength with sodium chloride. In the case of sodium ion, potassium chloride was used. Osmolar concentration was checked by the freezing point depression method with a differential thermometer.

After the experimental period—usually 20 minutes—the applied solution was withdrawn through the side-arm and the residual fluid was flushed from the eye with copious amounts of saline. The aqueous was immediately withdrawn with a 0.25-cc. syringe and 27-gauge needle and the eye was frozen by dropping into a beaker of hexane cooled in a dry-ice cellosolve bath.

In the cold room at -10°C ., the central corneal area which had been in contact with the applied solution was cut out with a cork borer and the remaining corneal annulus was cut out separately. Samples of the other ocular structures were dissected out and weighed at this time.

Samples were prepared for counting, and radioactivity was counted as described previously,⁵ with slight modification. Since the large-windowed Geiger-Müller tube used previously is no longer available, counting was done in steel cups of 2.5-cm. diameter

and a Tracerlab type TCG-2 Geiger-Müller tube was used. Correction was made for self-absorption where necessary.

B. DIFFUSION FROM A DEPOT PLACED IN CORNEAL STROMA

In this type of experiment a minute drop-let of labeled solution was placed in the center of the corneal stroma without damage to either epithelium or endothelium. This was accomplished with the aid of the microsyringe described previously.⁵ The 27-gauge needle was passed into the conjunctiva 1.0 mm. from the limbus and past the corneoscleral junction into the corneal stroma. The needle was then passed intralamellarily until its tip reached the corneal center. At this point one or two c.mm. of solution were injected and after a short wait the needle was withdrawn.

After a little practice using solutions containing a dye such as fluorescein this maneuver may be accomplished with surprising ease and accuracy and with no damage to either epithelium or endothelium. The rare eye that was so damaged was immediately detected and eliminated from consideration.

After injection, an applicator described in part A was immediately placed on the corneal surface centered over the minute depot and filled with 1.0 cc. of a solution of sodium chloride of known tonicity. The tonicity was varied from 0.7 percent to 1.6 percent. After the experiment was completed, usually at 20 minutes, the solution was withdrawn from the applicator, the applicator removed, an aqueous sample procured, and the eye frozen and dissected as before.

C. DIFFUSION FROM AQUEOUS HUMOR INTO CORNEA

In this type of experiment the microsyringe was used for injection of the anterior chamber as described previously,⁵ with some modifications. To eliminate the possibility of leakage of injected material, an annoying problem, we had formerly allowed the needle to remain in the eye for the dura-

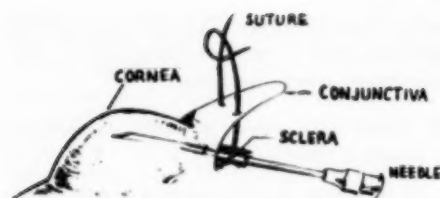


Fig. 2 (Potts). Technique of anterior chamber injection.

tion of the experiment. Cutting the needle off with a dull pair of pliers as suggested by Kinsey and Cogan changed the injected volume by a significant amount. A new and completely satisfactory technique is as follows:

A small (4.0 mm.) conjunctival flap is dissected at the limbus. Through the sclera so exposed, some 3.0 mm. from the limbus, is passed a double-armed suture of 5-0 black silk, forming a U-shaped loop penetrating half or more the scleral thickness but not perforating the globe. The arms of this suture are then passed through the conjunctival flap and looped once.

The injection is then made by the microsyringe, the needle entering the sclera 1.0 mm. peripheral to the suture loop and pass-

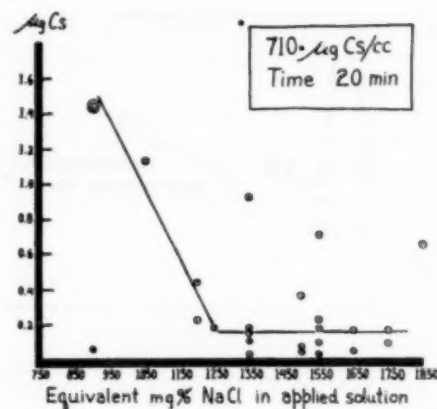


Fig. 4 (Potts). Inward diffusion of Cs^{134} (aqueous).

ing above it, through the limbus and into the anterior chamber. When the injection is completed, the loop is tightened over the conjunctival flap and needle and the latter is carefully withdrawn, tightening the suture as the needle leaves its channel to close the needle track instantly. The suture is then tied.

Figure 2 is a sketch of this arrangement. The procedure is quite effective in preventing leakage and is accomplished with a minimum of trauma.

RESULTS

The results of the experiments described are shown in Figures 3 to 11 and in Tables 1 to 3.

TYPE A

Experiments of type A, diffusion into the eye from solutions applied to the cornea, were done with sodium chloride labeled with Na^{22} , sodium phosphate labeled with P^{32} , and cesium chloride labeled with Cs^{134} . A control type of experiment was done with iodinated albumin labeled with I^{131} .

The results with labeled sodium are shown in Figure 3. It is easily discernible that as the osmotic strength of the applied solution increases, the penetration through the cornea goes through a minimum at a concentration

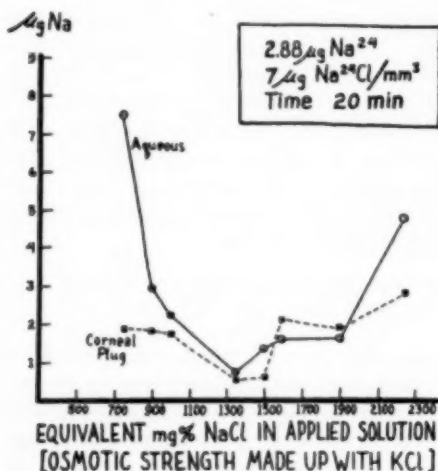


Fig. 3 (Potts). Inward diffusion of Na^{24}Cl applied to corneal surface.

TABLE 1

DISTRIBUTION OF INORGANIC IONS AFTER APPLICATION TO ANTERIOR CORNEAL SURFACE

Time: 20 minutes

A. Cesium

Composition of applied solution: 710 μ g. (5.3 μ mol.) Cs/cc.

	Micrograms Cs											
Osmotic equiv. as g. NaCl/100 cc.	0.75	0.90	1.05	1.20	127.5	1.35	1.50	1.55	1.65	1.75	1.80	2.00
Aqueous	1.28	1.41	0.85	0.35	0.07	0.93	0.36	0.20	0.14	0.16	0.64	0.41
		0.07		0.22		0.18	0.04	0.70	0.06	0.08		
				3.9		0.25	0.08	0.02		0.09		
						0.12	0.05	0.09				
								0.18				
Corneal Plug	0.998	1.22	0.69	0.45	0.30	0.85	0.41	0.43	0.14	0.46	0.84	1.12
		1.09		0.23		0.14	0.17	0.77	0.38	0.25		
				0.17		0.13	0.17	0.14		0.28		
						0.25	0.15	0.42				
								0.43				

B. Sodium

Composition of applied solution: 2.88 mg. Na (125 μ mol.) 7 mg. NaCl/cc.

	Micrograms Na											
Osmotic equiv. as g. NaCl/100 cc.	0.75	0.9	1.0	1.35	1.50	1.60	1.90	2.25				
Aqueous	7.46	2.98	2.13	0.845	1.39	1.62	1.60	4.7				
Corneal Plug	1.90	1.89	1.73	0.67	0.67	2.08	1.83	2.8				

C. Phosphate

Composition of applied solution: (1.34 mg. (14 μ mol.) PO_4 /cc.

	Millimicrograms PO_4											
Osmotic equiv. as g. NaCl/100 cc.	0.60	0.75	0.90	110	1.35	1.40	1.60	1.75	1.90	2.00	2.25	
Aqueous	178	330	697	1421	232	825	237	103	2320	33.8	298	
	703	191	1268	349	202	248	71	2290	132.5	64.5	209	
							58	143	30	1140		
										448		
										616		
Corneal Plug	296	686	1630	1695	495	655	385	255	126	91.5	114	
	2210	476	2672	1526	1051	1068	126	410	178.5	217.5	421	
							357	415	148	465		
										286		
										256		

equivalent to 1.35 percent NaCl. Beyond this point permeability appears to increase again.

In the case of cesium (fig. 4) and phosphate (table 1) it is again observed that permeability decreases to a minimum at approximately 1.35 percent. However, in the case of these two ions the increase of permeability with higher osmotic strength is not observed.

The penetration of sodium and cesium, though not great, is significant. The permeability to phosphate—a whole order of magnitude less—should be noted. That this is actual penetration is borne out by the fact that, when the applied solution contains

labeled iodoprotein, no activity is detectable in cornea or aqueous.

TYPE B

In the experiments on intracorneal injection the greatest amount of the injected material is recovered in the aqueous after 20 minutes. Irrespective of the variation in osmotic strength of the solution applied to the epithelial surface the amount recovered in this solution is less than 10 percent of the injected dose. This is true of sodium (fig. 5), iodide (fig. 6), and phosphate (table 2).

The difference between the sum of the corneal, aqueous, and supernatant figures and 100 percent is only in part accounted for

by diffusion to the posterior segment. An additional quantity must be accounted for by loss from the anterior chamber by aqueous outflow (see experiments of type C); the slope of the outflow curve is particularly steep for the first 20 minute period.

It should be noted that in the sodium experiments one is labeling a substance which is already present in large quantity whereas

in the case of the other ions there is no large amount of material already present. This seems to make little significant difference in the final results. However, it is difficult to be quite certain of the amount of mixing which takes place during the time of the experiment. For this reason results have been expressed in terms of the original dose only without reference to any additional sodium

TABLE 2
DISTRIBUTION OF INORGANIC IONS AFTER INTRACORNEAL INJECTION

Time: 20 minutes					
A. Iodide					
Injection consisted of: 1 mm. ³ solution containing 12.8 μ g. I (0.097 μ mol.) made isotonic with NaCl					
	Total Dose				
Osmotic equiv. as g. NaCl/100 cc.	0.9%	1.35%	1.6%	2.0%	
Aqueous	31.8%	22.2%	30.0%	27.0%	
	29.8%	35.3%	31.2%	37.8%	
Corneal Plug	2.5%	6.5%	6.8%	6.7%	
	11.3%	5.8%	7.2%	4.7%	
Applied Solution	18.6%	8.0%	2.8%	3.5%	
	5.3%	5.6%	2.1%	4.6%	
B. Sodium					
Injection consisted of: 1 mm. ³ solution containing 4.8 μ g. (0.082 μ mol.) Na					
	Total Dose				
Osmotic equiv. as g. NaCl/100 cc.	0.65%	0.9%	1.35%	1.7%	2.2%
Aqueous	30.1%	37.5%	52.1%	52.1%	54.3%
			47.6%		
			47.0%		
Corneal Plug	12.4%	16.7%	15.5%	11.7%	5.81%
			6.58%		
			15.94%		
Applied Solution	8.62%	8.57%	2.45%	8.53%	7.43%
			29.3%		
			1.46%		
Corneal Ring	2.93%	2.42%	3.6%	4.13%	3.95%
			6.7%		
			4.06%		
C. Phosphate					
Injection consisted of: 1 mm. ³ containing 3.14 μ g. (0.033 μ mol.) PO ₄ ; made isotonic with NaCl					
	Total Dose				
Osmotic equiv. as g. NaCl/100 cc.	0.8%	1.35%	1.5%	1.6%	2.0%
Aqueous	25.6%	33.7%	31.0%	36.8%	44.3%
	40.1%	35.2%		33.9%	48.8%
		41.6%			
		34.0%			
Corneal Plug	31.8%	40.0%	42.0%	41.4%	30.4%
	19.9%	28.0%		43.9%	26.7%
		35.3%			
		31.4%			
Applied Solution	2.32%	2.7%	1.81%	0.165%	0.75%
	6.30%	9.0%		0.193%	1.39%
		5.6%			
		1.48%			
Corneal Ring	2.08%	3.9%	2.47%	3.24%	3.4%
	2.72%	2.3%		1.93%	3.1%
		3.3%			
		3.7%			

which may have been labeled. Relative figures will not be affected by this but it should be borne in mind that absolute figures are considerably higher.

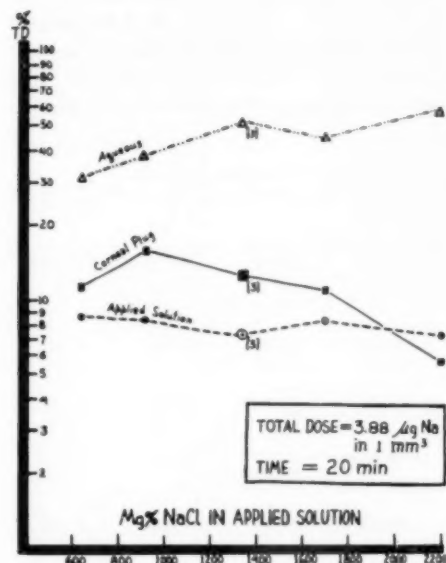


Fig. 5 (Potts). Outward and inward diffusion of Na^{24} injected intracorneally.

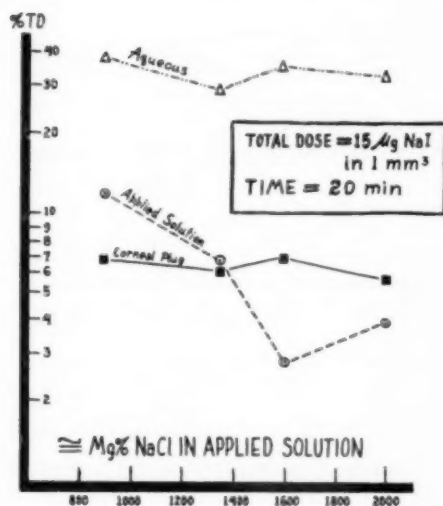


Fig. 6 (Potts). Outward and inward diffusion of I^{131} injected intracorneally.

Here, too, when radioactive iodoprotein is injected intracorneally by this technique, only a negligible number of counts is detectable in either the aqueous or the applied solution. In both the case of the inorganic ions and the labeled protein, the corneal outer ring concentration never exceeds 25 or 30 percent of the amount left in the center plug.

TYPE C

In this type of experiment the rate of outflow appeared to follow the expected logarithmic form except that a sharp change in slope occurred at about 20 minutes in the case of each ion tested (sodium, Figure 7; phosphate, Figure 8; and iodide, Table 3). The early part of the experiment is complicated by the fact that diffusion throughout the anterior chamber is not complete for five to 10 minutes. A trial run with 1.0 mm.³ of 2.0 percent sodium fluorescein shows an irregular pattern of diffusion whose outline appears as shown in Figure 9. Two eyes are shown here and the variation between the two is typical.

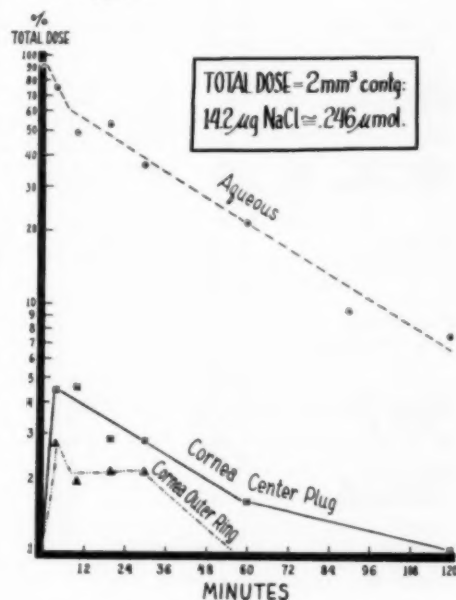


Fig. 7 (Potts). Na^{24} exchange after injection into anterior chamber.

When the outflow figures are calculated as μ moles per gm. (or cc.) and plotted on linear coördinates (fig. 10, fig. 11, table 3), the concentrations of aqueous and cornea are seen to approach each other and, although in the case of sodium they never actually become equal, in the case of phosphate and iodide these concentrations are virtually identical after 30 to 40 minutes.

DISCUSSION

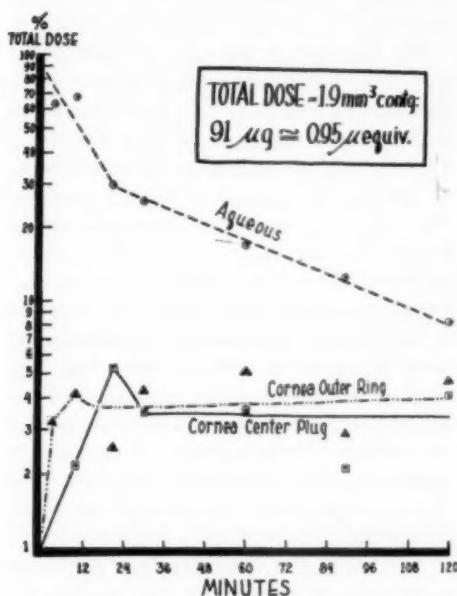
The results in the external application experiments (type A) indicate that the osmolar concentration for minimum corneal permeability is equivalent to 1.35 percent sodium chloride and above. One may assume that the lower osmotic concentrations cause sufficient damage to the corneal epithelium to

TABLE 3
DISTRIBUTION OF INORGANIC IONS AFTER INJECTION INTO ANTERIOR CHAMBER

A. Sodium							
Total dose: 1 mm. ³ containing 7.1 μ g. = 0.123 μ mol.							
Time	4 min.	10 min.	20 min.	30 min.	60 min.	90 min.	120 min.
Aqueous	71.3	49.7	54.0	37.1	24.3	9.36	7.7
% total dose	77.3		46.5		18.9		
	73.0						
Aqueous	0.702	0.488	0.532	0.365	0.239	0.092	0.076
μ mol./cc.	0.760		0.457		0.186		
	0.718						
Corneal Plug	4.95	4.58	2.70	2.81	1.60	0.53	1.00
% total dose	5.04		3.05		1.48		
	3.04						
Corneal Plug	0.403	0.303	0.218	0.209	0.127	0.037	1.107
μ mol./g.	0.219		0.256		0.046		
	0.369						
Corneal/Ring	3.38	1.95	1.84	2.18	0.914	0.468	0.588
% total dose	3.07		2.55		0.965		
	1.68						
Corneal/Ring	0.299	0.174	0.181	0.194	0.088	0.038	0.052
μ mol./g.	0.313		0.244		0.082		
	0.092						
B. Phosphate							
Total dose: 1.9 mm. ³ containing 91 μ g. 0.95 equivalent							
Time	4 min.	10 min.	20 min.	30 min.	60 min.	90 min.	120 min.
Aqueous	53.0	68.6	29.9	25.7	18.05	18.6	8.38
% total dose	73.5					5.41	
	47.6					15.0	
	78.0						
Aqueous	0.180	0.261	0.114	0.163	0.0572	0.0590	0.0318
μ mol./g.	0.465					0.0171	
	0.296					0.0475	
	0.191						
Corneal Plug	0.83	2.16	5.33	3.5	3.65	2.73	4.15
% total dose	1.10					1.47	
	0.56					1.09	
	0.42						
Corneal Plug	0.0235	0.0595	0.147	0.099	0.108	0.0620	0.097
μ mol./g.	0.0271						
	0.0156						
	0.0122						
Corneal Ring	6.4	4.17	2.6	4.3	5.1	3.0	4.68
% total dose	1.15					2.82	
	2.65					1.31	
	1.78						
Corneal Ring	0.092	0.092	0.050	0.076	0.086	0.038	0.073
μ mol./g.	0.0164						
	0.053						
	0.0264						

TABLE 3—(continued)

C. Iodide										
Total dose: 1 mm. ² containing 6.88 μ g. I=0.052 μ mol.										
Time	4 min.	10 min.	20 min.	30 min.	40 min.	60 min.	80 min.	90 min.	100 min.	120 min.
Aqueous % total dose	76.3 70.0 66.8	45.0	26.8 20.9 10.9	27.3 11.0 14.4	13.3	4.72 15.3 12.9	9.65	5.31	0.88 2.35	1.35 3.54
Aqueous μ mol./cc.	0.159 0.121 0.073	0.094	0.073 0.054 0.023	0.057 0.026 0.038	0.028	0.0098 0.040 0.034	0.022	0.011	0.0023 0.0060	0.0023 0.0092
Corneal Plug % total dose	1.81 1.12 3.02	1.48	3.02 2.38 1.39	2.46 2.57 2.12	2.50	0.52 2.18 2.15	1.45	1.30	0.57 0.81	0.33 0.61
Corneal Plug μ mol./g.	0.031 0.015 0.043	0.021	0.043 0.046 0.023	0.038 0.036 0.030	0.039	0.0089 0.032 0.029	0.021	0.019	0.0082 0.0012	0.0037 0.0056
Cornea Ring % total dose	1.38 4.33 2.54	1.16	2.54 3.06 1.04	1.89 1.71 2.37	1.85	0.57 2.37 1.68	0.79	1.29	0.54 0.85	0.40
Cornea Ring μ mol./g.	0.025 0.037 0.032	0.020	0.032 0.033 0.021	0.039 0.021 0.029	0.019	0.0074 0.027 0.021	0.0133	0.014	0.0072 0.0085	0.0035

Fig. 8 (Potts). $P^{32}O_4$ exchange after injection into anterior chamber.

allow increased penetration of the ions in question. Thus these results agree with those of Massart and Nakamura and the recently published contact-lens experiment of Kinsey¹² that the precorneal tear film is hyper-

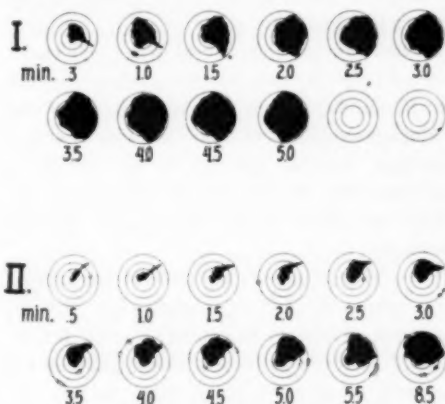


Fig. 9 (Potts). Diffusion of fluorescein injected into anterior chamber.

tonic and equivalent osmotically to a 1.35 percent NaCl solution.

In the choice of optimal osmotic concentration for medication, one must compromise between desired penetration and corneal damage. One knows that minimum penetration of ionized substances occurs at 1.35 percent sodium chloride equivalent and above and, if adequate amounts of medication penetrate the eye under these conditions, ophthalmic solutions of such medications

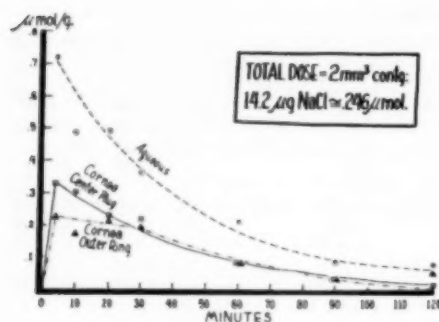


Fig. 10 (Potts). Loss of Na^{25}Cl from anterior chamber.

should be made up to this osmolar strength. If greater penetration is desired, it may be obtained at the expense of some corneal damage by using a solution hypotonic to the figure just quoted.

The results of the corneal injection experiments (type B) indicate that a relatively very small number of the injected ions enter the solution applied to the anterior corneal surface. This is parallel to the outside-in permeability of the corneal epithelium and was remarked in the first paper of this series.⁷

As already noted, the bulk of the labeled ions move through the endothelium into the aqueous. There is little tendency for the injected material to move centrifugally in the cornea, as it must do if there were a re-entrant circulation of inorganic salts. The fact of transfer of most of the material into the aqueous does not alone indicate that there is a net transport of salts from cornea to aqueous as a continuous mechanism. The same result could be achieved by simple diffusion, for labeled ions are only present on one side of the cornea.

When, however, one takes into account the rapid entrance of ions from the blood to the cornea and the lack of tendency for diffusion peripherally in the cornea, such an active transport mechanism seems likely. This would be a solution to the problem of what becomes of the corneal salts.

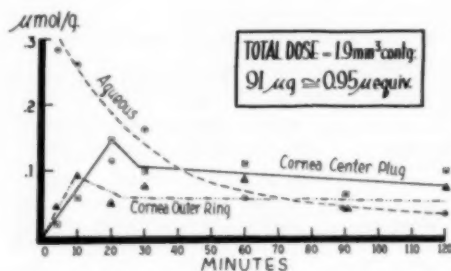


Fig. 11 (Potts). Loss of P^{32}O_4 from anterior chamber.

We believe that the failure of labeled protein to leave the cornea in significant quantities is adequate demonstration of the mechanical integrity of the endothelium. The relatively rapid rate of diffusion of protein in ocular structures where no membrane exists has been demonstrated previously.¹²

The findings of the type C experiments tend to throw some question on the active transport of ions from cornea to aqueous as against simple diffusion in both directions. That there is penetration of the endothelium by salts in the aqueous is beyond question. The apparent equilibria demonstrated in Figure 11 and Table 3 after 30 or more minutes indicate that simple diffusion may actually be taking place. However, it should be noted that with sodium, equilibrium is never attained and with the other ions it is reached only at low levels when most of the injected material is gone. A differential rate of transport from cornea to aqueous as against aqueous to cornea may exist, but further experiments are required to decide this point.

Any help that mathematical treatment might give is clouded by the question of mixing. In experimental types B and C the question of mixing is an important one. As is seen in Figures 7 and 8 the outflow rate after 20 minutes is close to the expected exponential function, but mixing irregularities as shown in Figure 9 obscure the early relationships. For this reason applying a mathematical formulation to events of the

first 20 minutes could very well be misleading, and a more useful approach is the empirical investigation of a sufficiently large number of eyes to give reliable results.

At this point we do not feel justified in postulating active transport of inorganic salt (and accompanying water) from cornea to aqueous. However, we have demonstrated the relatively rapid transfer of inorganic ions across the corneal endothelium, particularly in the cornea-aqueous direction. This is incompatible with the Cogan-Kinsey theory as it is now formulated.

The corneal epithelium is truly a membrane poorly permeable to salts in both directions but the endothelium is not such a membrane. It is hard to believe that the normal flow of tears is adequate to maintain deturgescence alone. If the endothelium proves to be equally permeable to salts and water in either direction one will be hard put to it to explain corneal deturgescence on any theoretical basis. At the moment further generalization must await additional experimental results.

SUMMARY

1. Experiments have been reported which demonstrate the rate of transfer of inorganic ions across the corneal epithelium and endothelium in both directions.

2. Results of these experiments indicate that in agreement with previous work the corneal epithelium has low permeability to inorganic salt in both directions.

3. In contrast to this the corneal endothelium is relatively freely permeable to salts, certainly from cornea to aqueous and possibly from aqueous to cornea.

4. These findings require revision of presently accepted theories of corneal dehydration mechanisms.

5. The osmotic concentration which does least damage to the corneal epithelium is equivalent to 1.35 percent sodium chloride. This by inference is the tonicity of tears.

Western Reserve University (6).

I wish to thank Miss Doris Goodman for the illustrations and graphs in this paper.

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DISCUSSION

DR. DAVID G. COGAN (Boston): Dr. Potts was good enough yesterday to brief me as to his general thesis, and I think he and I both wound up by being somewhat confused by two seemingly clear bits of experiments that would indicate opposite conclusions.

In the first place, his studies have indicated that the endothelium is relatively freely permeable to sodium and to other ions, and the technique he uses would suggest that there isn't any real evidence that he damages the endothelium by his procedure.

One might raise the objection that the injection of labeled albumen is an insufficient test, if it is done in 20 minutes, because the limiting factor may be the diffusion rate of albumen in the cornea. It might be worthwhile checking that further with some more readily diffusible dyes or something that has a diffusion rate similar to that of electrolytes.

There is no real evidence, however, that the endothelium is damaged, and yet it appears to be permeable to these ions in both directions in the living animal. The experiments Dr. Kinsey and I did on enucleated eyes indicated that the epithelium is impermeable to electrolytes, as Dr. Potts has also shown.

The endothelium is less readily amenable to experimentation, in that one can't excise a cornea and put it on the end of a tube without damaging the endothelium. If you touch it with your finger the endothelium comes off and a slight trauma is devastating, so it can't be subjected to the same experimental technique.

We used the whole eye, however, by putting a tube on the surface of the cornea, in a watertight manner, and then putting a cannula into the anterior chamber through the posterior portion of the eye. The epithelium was removed purposely but care was taken not to traumatize the endothelium since the stroma and Descemet's membrane were known to be freely permeable, we were able in this way to test the barrier properties of the endothelium.

We found that water was transferred into the eye regularly as long as the fluid in the anterior chamber was hypertonic to that in the cornea. No net water was transferred when the endothelium was removed. That indicated that the endothelium was the effective semipermeable membrane with respect to sodium chloride, for the enucleated eye.

Dr. Potts's observations and ours seem to be contradictory. Our experiments were done on the enucleated eye, and his were done on the living eye, but the results one would expect in the enucleated versus the living eye are just the opposite of what occurred. One could readily conceive that a membrane would be impermeable during life, and then at death would lose its barrier properties and become freely permeable, but the opposite is here the case.

Dr. Potts finds that the membrane in the living animal is readily diffusible, and we find in the enucleated eye that it is impermeable. I think it is clearly a contradictory set of experiments, and it will be very interesting to find out in future studies

what the explanation of this is. They are both simple, straightforward experiments which anyone can repeat, and we hope they will be repeated.

DR. LUDWIG VON SALLMANN (New York): Does Dr. Potts think that the local anesthetic used could have changed the permeability of the endothelium? Dr. Cogan used no local anesthesia in his experiments. May I ask what compound was used for this purpose in Dr. Potts' experiment?

Another question is whether the intracorneal injection of even a small quantity of fluid with a 27-gauge needle does not alter the permeability of the endothelium in view of the considerable trauma it inflicts upon this structure.

DR. POTTS: These animals were under nembutal anesthesia. That cannot be avoided. We did sometimes use local anesthetics, and we found no difference in the results between using a small amount of local anesthetic and using none.

Ordinarily the nembutal was adequate to take care of the situation. For this reason the nembutal effect may be a very real one; and that we can't avoid, although using a living animal is different from using an enucleated eye. I don't quite know how to keep an applicator on the cornea for 20 minutes without some type of anesthesia.

As far as the trauma is concerned, I would expect to see large quantities of material, even of the injected protein, enter the aqueous if trauma occurred. I should have mentioned that an occasional accident happens, and there is no question about the accident when it occurs, because the content of the corneal plug is zero or virtually zero. The content of the aqueous is also much higher in these experiments.

Such accidents are very easily detected; they represented perhaps one twentieth of all the eyes done, and had to be discarded.

The authors wish to thank Dr. Cogan for his many helpful comments. A number of his suggestions will be employed in an attempt to reach a solution of our discrepant results.

DR. COGAN: Pursuing the possibility that trauma does in some way have something to do with results, I would like to suggest that you repeat the experiments and, instead of injecting into the cornea, remove the epithelium and put the cup with the solution on the surface of the eye, and then test the aqueous. It is possible that the injection in some way does damage the endothelium.

Is it possible that the tonicity of the fluid you inject is hypertonic to that of the aqueous? That would damage the endothelium. What was the tonicity?

Dr. Potts tells me he is going to try another experiment in which he will compare his results with the same experiments in which the endothelium has been purposely removed beforehand.

DR. POTTS: The tonicity was adjusted to 0.9 percent.

DIRECTION SENSE OF THE EYE*

ELEK LUDVIGH, PH.D.

Detroit, Michigan

For almost a century the remarkable accuracy of what Bourdon¹ has called the direction sense of the eye has been known. The tests of this so-called sense are, in fact, tests of the perception of relative direction. Thus, in the alignment or vernier test the lower of two lines is stated to be situated to the right or to the left of the upper line and the displacement necessary to permit such a statement to be correct is a measure of the accuracy of the perception.

Similarly, in the contour break test the lower edge or contour is perceived as to the right or to the left of the upper one.

In stereoscopic vision, a similar percept of direction is involved, but here, as in the Howard-Dolman test, for example, the lower line is perceived to be closer to or farther away from the observer than is the upper line.

If, however, during the performance of the Howard-Dolman test, the left eye be situated in the vertical plane passing through the two rods, then the resultant perception of depth, which is not substantially impaired under these conditions, is entirely dependent upon an alignment or contour break test presented to the right eye.

In all these tests it can be shown that, under favorable conditions, an angular discrepancy of two seconds of arc may reliably be perceived and discriminations of the order of one second of arc, or even somewhat less, may occur with a frequency inexplicable on the basis of chance.

Since an average size human foveal cone subtends about 30 seconds of arc at the nodal point of the eye, and since even the smallest cones subtend about 12 seconds of arc,² it has long been apparent that this type of acuity or direction perception is not limited, as Snellen acuity or two-point dis-

crimination may be, by the width of a retinal element.

Efforts have been made by Hering,³ Bourdon,⁴ and Cowan,⁵ among others, to explain perception accurate to fractional cone widths, but explanations of this type have failed when consideration is taken of the fact that the accuracy of these tests is substantially independent of slight variations of orientation from the vertical, that diffraction and aberration produce a blur disc the angular diameter of which is of the order of two minutes of arc on the retina⁶ and that the eye is in a constant state of tremor.^{7, 8}

The presently prevailing hypothesis is that of Anderson and Weymouth.⁹ Their explanation is illustrated by Figure 1. The circles represent foveal cones, the dark area to the left is the edge of a line. This dark edge may move from position A to position B as a consequence of the fixation tremor of the eye.

Some, but not necessarily all, of the cones between the lines A and B or touching them may be stimulated. The position of the cones stimulated is then averaged and the position of the edge is taken to be at the line M. To this percept of the line M, Anderson and Weymouth give the name "retinal mean local sign."

They point out that, just as a measurement may be made accurate to a fraction of an inch, even though the measuring rule may be read only to the nearest inch, by taking repeated measurements and averaging them, so the mean local sign may be found with an error substantially smaller than the width of a cone.

It is emphasized that, in order to obtain an accurate average, a large number of cones must be involved, and it has been shown that, if the length of contour¹⁰ or length of line or length of rod⁹ be made to subtend

* From the Kresge Eye Institute.

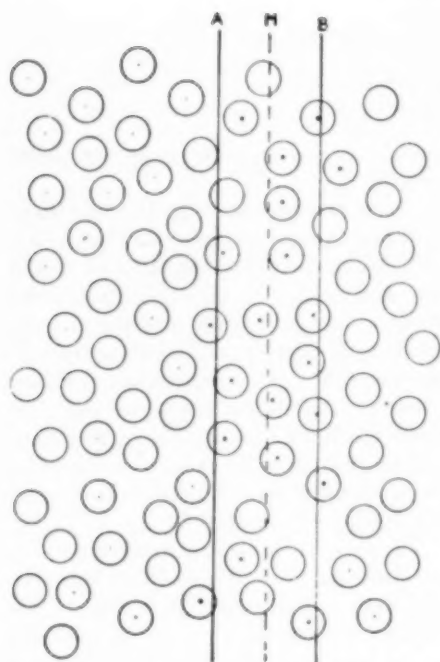


Fig. 1 (Ludvigh). A graphic explanation of the hypothesis of Anderson and Weymouth.

a small retinal angle, the performance seriously deteriorates.

Further possible amplifications of the Anderson-Weymouth hypothesis, such as assuming that the retinal elements involved are on-off elements operating at borders only, "neural peaking," and reliance upon the expansion or magnification of the retinal image in the cortex by reason of the divergence of the pathways on the way to the visual cortex make the hypothesis more tenable.

Bourdon found that a test object consisting of three short vertical lines separated by two short vertical gaps could be aligned with high accuracy.

In the present experiment, the lines have been contracted to dots of light, the angular separation of the top and bottom dots has been varied, and the accuracy with which the middle dot could be aligned with the other two has been determined.

Figure 2 shows the accuracy of performance of one observer* on this test at the 75-percent correct level as tested by the classical method of right and wrong cases with forced guesses. Each point is based on 96 observations, the duration of each observation was five seconds or less. Observations were taken monocularly and Snellen acuity was 20/15. The height of bar represents two probable errors at each point.

On the x axis is plotted the angular separation between the top and bottom dots measured in minutes of arc at the nodal point of the observing eye. On the y axis is shown the lateral displacement in seconds of arc of the central dot necessary to produce 75-percent correct judgments.

It can be observed that, when the separation of the two dots is 10 to 20 minutes of arc, a lateral displacement of approximately two seconds suffices to produce 75-percent correct judgments. The odds against 75-percent or more correct judgments out of 96 occurring by chance are approximately four million to one. The odds against even 63-percent correct judgments occurring by chance are in excess of one hundred to one and 63-percent correct judgments are obtained with a displacement of about one second of arc.

If a foveal cone be assumed to subtend 40 seconds of arc at the nodal point of the eye, then this result means that a retinal image displacement of one fortieth of a cone width can be perceived when the two reference images on the retina are separated by 30 cone widths.

If one wishes to assume that the smallest central foveal cones might subtend as little as 10 seconds of arc, then one tenth of a cone width on the retina can be perceived when the reference images are 120 cone widths apart.

Furthermore, as the angular separation of

* A second observer gave substantially similar results which are omitted in order to simplify the figure.

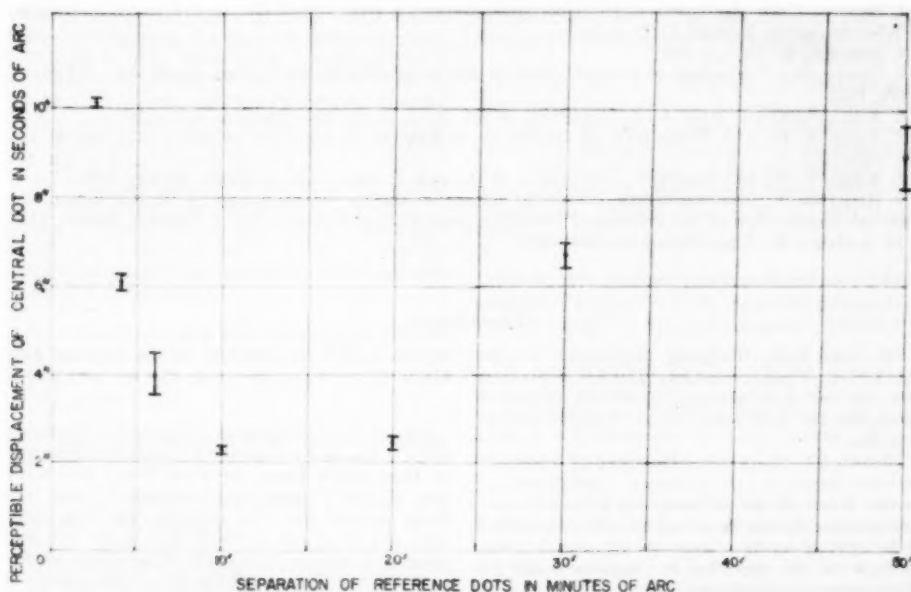


Fig. 2 (Ludvig). Accuracy of performance of one observer on the test.

the reference dots is increased from 2.5 minutes to 20 minutes of arc the discrimination improves from 10 seconds to two seconds of arc, although no greater number of cones is stimulated in the latter instance than in the former.

If an hypothesis can be found to explain the high degree of accuracy of this three-dot alignment test, as well as its improvement with increasing separation of the reference dots, then such an hypothesis would presumably also be adequate to account for the improvement of the contour break, vernier and depth perception test with increasing height of line.

Furthermore, since the accuracy of the three-dot alignment cannot be explained in terms of averaging the mean position of a statistically large number of cones, it seems likely that this hypothesis does not, in fact, account for the accuracy of the contour

break, vernier, and stereoscopic tests.

Even the assumption of perfect neural peaking and a 10,000-fold areal expansion of the fovea in the visual cortex still leaves the problem unsolved. If the cortical elements involved are taken to be as small as cones, a displacement of one second would now correspond to a width of two cortical elements.

Perfect neural peaking would result in one cortical element being stimulated rather than the 30,000 which aberration, diffraction, and fixation tremor would stimulate in the absence of peaking. However, the problem would remain as to how the displacement of two cortical elements could be perceived when the reference dots stimulated cortical points 300 cortical elements apart.

It is difficult to see how the data here presented can be accounted for other than in terms of a field theory of some type.

690 Mullett Street (26).

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DISCUSSION

DR. HUGO BAIR (Rochester, Minnesota): I think Dr. Ludvigh's paper certainly presents a problem to us, not only with reference to ordinary monocular perception but with reference to binocular perception also.

Undoubtedly, there is a relationship of some sort between stereopsis and monocular displacement or vernier acuity. When the perception is binocular one can theoretically say there may be a distinction that is brought about by virtue of the stimuli going through the two eyes; but in the present case the phenomena are entirely monocular.

"Direction sense" is not a good term to describe this, yet I can think of none better. It certainly is not "acuity" in the sense of the two-point limen of the skin. It is acuity in a more general sense.

As Dr. Ludvigh mentioned, the explanation may resolve itself into some sort of field theory. I am not competent to try to discuss that, but at least that would seem to place it beyond the level of retinal function itself.

I did experiments some time ago on the ordinary contour-break phenomenon, on resolving power, and on the minimum visible thin black line, and found the same sort of behavior; namely, that the acuity increased as a definite function of the length of the lines.

To explain the contour-break phenomenon, one might invoke the same idea that Anderson and Weymouth had; that is, some sort of mental averaging of the positions of the contours; but actually the contour-break itself should not be affected by such a process. The same thing holds for vernier acuity.

I think this is an interesting paper, and certainly should stimulate further investigation along similar lines.

DR. LUDVIGH: I agree with Dr. Bair that the direction sense is an inappropriate name. That is what Bourdon called it in his "La perception visuelle de l'espace."

The tests of this so-called "sense" are in fact the tests of the perception of relative direction. In other words, it is really a percept rather than a sense, and this very high accuracy, of course, is a relative one only. One's knowledge of the absolute location of an object in space is, of course, ex-

remely fallible as compared to the accuracy with which this relative direction can be ascertained.

DR. H. L. UNDERWOOD (Vancouver, Washington): I was at the Hazelhurst Research Laboratory on Long Island during the First World War while the Howard-Dolman depth-perception test was being worked out. The problem was that, since stereopsis is an aid to the flyer, a better test than using a stereoscope to rate depth-perception should be developed. The standard in the aviation service in 1918 depended upon the use of the stereoscope and the German slides.

As a result of that research, that method gave way to the Howard-Dolman depth-perception test. They found it advisable to exclude the element of distance as derived from consideration of motion parallax and variations in size due to distance; therefore they covered both the lower and upper extremities of the two pencils used in the test, in order that they might depend entirely upon stereopsis and alinement.

Distance was taken at 20 feet, the subject himself performing the manipulation and bringing the targets to an equal distance by means of cords attached to the movable target bases.

The objective was to make a test of the flyer's capacity for prompt and accurate estimate of distance and to exclude or accept him, the rating being an error of 5.0 mm. for excellent; 8.0 to 12, average; and 15 maximum, allowable. The standard may have been changed since. It seemed to me that it was a useful test at the time and more effective for our purposes than the use of the stereoscope alone, in that it more nearly simulated flying conditions.

The element of psychic interpretation comes into consideration of visual judgment, as well as "experience" factors: namely, parallax and dimensional changes during motion, which were, as stated, excluded purposely. However, these are useful, and, in one-eyed subjects, essential.

DR. KENNETH OGLE (Rochester, Minnesota): Were you using black dots against a white background?

DR. LUDVIGH: No; these were white dots against a black background. In fact, it consists of small drill holes in three brass plates. These subtend at the nodal point of the eye three seconds of arc at a distance of 71 feet, which is the distance at which the test is conducted. The central dot also consists of a hole illuminated by a fluorescent lamp from the rear. This hole is in a brass plate.

The brass plate is displaced by means of a spring-loaded lead screw. The apparatus is calibrated by putting a Western Union light source, 0.003 inches in diameter, behind the entire assembly, projecting it up 50 times, and then measuring up to determine where the zero actually is.

DR. OGLE: These dots were seen against a fairly black background?

DR. LUDVIGH: Yes.

DR. OGLE: So the image would be comparatively large?

DR. LUDVIGH: No question about it. There is a substantial diffraction disc.

DR. OGLE: There would be at least seven or eight retinal elements involved in this judgment?

DR. LUDVIGH: There are numerous retinal elements being stimulated, no doubt, by each dot; but substantially no more when the dots are separated by 50 minutes of arc than when they are separated by five.

DR. OGLE: You didn't try changing the intensity of the background so that you reduced the contrast,

to reduce the size of the blur on the retina and therefore involve fewer retinal elements?

DR. LUDVIGH: No. This was all done at substantially high brightness. If I were to reduce the brightness, I would decrease the effective radius of the diffraction disc somewhat, of the aberration disc substantially. There would not be much you could do about the fixation tremor except to shorten the exposure, and when you do that peculiar things happen.

DR. K. W. ASCHER (Cincinnati, Ohio): Did I understand properly that the vernier acuity increases when the length of the lines compared increases?

DR. LUDVIGH: Yes. Dr. Bair tells me he has done it for the contour break. I have done it for the vernier acuity, and Anderson and Weymouth have done it for stereopsis. In each instance the accuracy improves as the length of the line increases.

DR. ASCHER: It is possible that the length of the exposed line influences the physiologic nystagmus of the eye in the sense of fixating the eye more properly if a longer line is exposed, as compared to the fixation enforced by fixation of a shorter line?

DR. LUDVIGH: Dr. Adler has done some experiments on fixation tremor with varying lengths of line. In his absence my recollection is that he finds that the fixation tremor does decrease somewhat in amplitude as the fixation target is made more suitable. That is a potential factor in the contour-break alinement and stereoscopic test, but it can't account for this three-dot test.

CATARACTS CAUSED BY CARBOHYDRATES*

JOHN W. PATTERSON, M.D.
Cleveland, Ohio

High blood levels of glucose,^{1,2} xylose,³ or galactose^{4,5} produce cataracts. In order to obtain the high levels necessary for the production of cataracts the physiologic mechanism for utilizing or excreting these substances must be overloaded. In the case of glucose, this is accomplished by producing diabetes and in the case of xylose and galactose by feeding diets which contain excessive amounts of these sugars.

Cataracts produced by glucose, galactose,

or xylose are qualitatively similar. They are alike in appearance⁶ and their development is affected in the same manner by age. Thus, the younger the animal the more readily diabetic cataracts,⁷ and galactose cataracts⁸ develop. This is apparently also true of xylose cataracts for this type has only been produced in very young rats.^{3,9}

Galactose and xylose¹⁰ are accepted as producing cataracts by some mechanism related to the high blood sugar. However, the mechanisms proposed for the production of diabetic cataracts are more varied. Since

*From the School of Medicine, Western Reserve University.

hyperglycemia, acidosis, neoglycogenesis, lack of insulin, and deranged carbohydrate metabolism are all associated with diabetes, any one of these factors might be important in the production of cataracts.

Since diabetic cataracts may be prevented by lowering the blood sugar with phlorizin,¹¹ or with a high-fat diet,^{7,12} the prime importance of the high glucose level becomes evident. Phlorizin does not improve any of these factors excepting the high blood sugar. Therefore, it would appear that glucose may act in a manner similar to galactose and xylose.

This paper is concerned with relating galactose and glucose cataracts by demonstrating that these substances may act in a synergistic manner and in presenting evidence that suggests a mechanism by which sugars may produce cataracts.

EXPERIMENTAL

Three groups of male Sprague-Dawley rats were placed on different regimes and followed with regard to the severity of their diabetes and the time required for cataract formation. The severity of the disease was estimated by averaging weekly blood-sugar determinations and the eyes of the rats were observed for cataracts daily as previously described.¹

A group of eight rats was given diabetes by injecting 40 mg. per kg. of alloxan monohydrate intravenously. These animals were then placed on a diet containing 20-percent galactose and 80-percent ground dog chow (Friskies) and maintained on this diet until cataracts developed. The other two groups of rats served as controls.

One group of four rats served as the diabetic control. After the injection of alloxan, these rats were maintained on a diet free of galactose. The second group of eight rats served as galactose controls for they received the 20-percent galactose diet but were not injected with alloxan.

The diabetic rats that received 20-percent galactose developed cataracts in 35 to 60

days with an average time of 46 days and a standard deviation of eight days. The diabetic controls required 61 to 77 days or an average of 66 days, with a standard deviation of seven days for cataract formation.

The eight galactose controls were followed for 84 days and at this time 50 percent of the rats had not developed cataracts. However, four rats developed cataracts in 64 to 76 days. If, for the sake of calculation, the four galactose control rats that did not develop cataracts were assumed to have cataracts at 84 days, the average time becomes 75 days with a standard deviation of 11 days.

The diabetic rats that received 20-percent galactose developed cataracts significantly sooner than either control group. The *P* value when compared with the controls was less than 0.0001 in each case (fig. 1).

It was postulated that high carbohydrate levels produced their effect by blocking the cellular absorption of some essential metabolite.^{1,13} This could be the result of competition for cellular energy or a limiting enzyme system. Since phosphates^{14,15} and ascorbic acid¹⁶ were known to compete with glucose for absorption, supplements of these substances were administered to determine their effect on the development of cataracts.

Eight rats weighing between 114 to 150 gm. were injected with alloxan and given potassium-phosphate buffer containing 0.42 gm. of phosphate per 100 cc. at pH 7.0 to

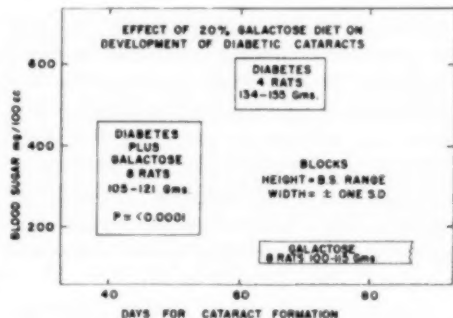


Fig. 1 (Patterson). Effect of 20-percent galactose diet on development of diabetic cataracts.

drink in place of their regular drinking water. They were maintained with this as the only source of fluid until cataracts developed between 68 to 110 days. The time averaged 81 days with a standard deviation of 13 days.

Compared with animals with equally severe diabetes¹¹ there was no significant delay in cataract formation (fig. 2).

Seven rats weighing 168 to 202 gm. were injected with alloxan and subsequently injected intravenously twice each week with 200 mg. per kg. of dehydroascorbic acid. This substance penetrates cells rapidly and is reduced to ascorbic acid, producing a marked increase in the cellular level of this compound.¹² During this period, the average blood sugar, determined before an injection of dehydroascorbic acid, was 565 mg. per 100 cc.

After cataracts had developed in 75 to 103 days with an average of 81 days and a standard deviation of nine days, the injections of dehydroascorbic acid were stopped and the blood sugars were determined over a period of weeks.

During this period the average dropped to 476 mg. per 100 cc. Since the P value for this change was less than 0.05 it indicated that the diabetes was more severe during the injection period. Increasing the ascorbic acid level of the cells in this manner did not significantly delay the appearance of cataracts (fig. 2).

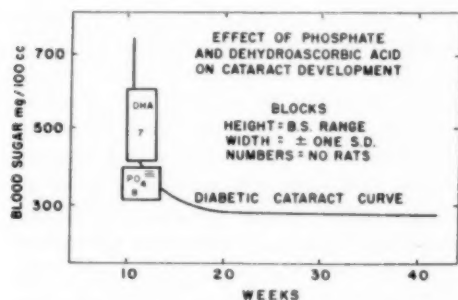


Fig. 2 (Patterson). Effect of phosphate and dehydroascorbic acid on cataract development.

EFFECT OF SUPPLEMENTAL FEEDING ON DEVELOPMENT OF GALACTOSE CATARACT

NO RATS	4	4
DAYS OF WEEK	SMWF	TTS
35% GALACTOSE Gms./day	20 10	20 10
CHOW DIET Gms./day	20 10	20 10
H ₂ O INTAKE cc/day	50 25	50 25
URINE VOLUME cc/day	30 10	30 10
URINE SUGAR Gms./day	1.5 0.5	1.5 0.5
WEIGHT GAIN 9 weeks	195	0
CATARACTS	none at 116 days	40 ± 3 days

Fig. 3 (Patterson). Effect of supplemental feeding on development of galactose cataract.

If, as postulated, high blood-sugar levels blocked the cellular absorption of some essential metabolite, and if this metabolite was only available to the cell at the times when the blood sugar was elevated, then one should not expect to prevent cataracts and thus demonstrate the nature of this substance unless it was provided when the blood-sugar values were normal.

This would be especially true if the cell had a much stronger affinity for sugar than for the unknown substance. To test this reasoning and to obtain evidence that cataracts resulted from a metabolic deficiency the following experiment was tried:

Two groups of rats weighing 55 to 134 gm. were placed on identical regimes of 35-percent galactose plus 65-percent ground chow. This was given to the rats on Sunday, Monday, Wednesday, and Friday. These animals ate 20 gm. a day.

On Tuesday, Thursday, and Saturday, however, the rats were treated differently. One group of four rats received 20 gm. of normal chow on these days and the other group of four rats was starved. The results have been summarized in Figure 3.

The water consumption followed the food intake and the urine volume in turn followed

the water intake. The reducing sugar in the urine was related roughly to the galactose in the diet. However, the starved animals spilled slightly more sugar than the rats that were fed the supplemented diet. The weight gained reflected the caloric intake.

The rats receiving the supplemented diet did not develop cataracts, whereas, the rats receiving the same amount of 35-percent galactose without any supplement developed cataracts in 37 to 45 days with an average of 40 days and a standard deviation of three days.

DISCUSSION

Since the lowering of the blood sugar of diabetic rats with insulin,^{12, 13} a high-fat diet,^{7, 12} a high protein diet,¹² or phorizin¹¹ prevents or delays cataract formation, it seems probable that the high level of glucose is the important etiologic factor in the development of diabetic cataracts. This places diabetic cataracts in the same category with those produced by galactose and xylose. The fact that glucose and galactose act in a synergistic manner adds additional support to this viewpoint and indicates that a common mechanism is involved in the production of diabetic and galactose cataracts.

Preliminary results indicate that xylose acts in a fashion similar to galactose. These observations are very useful in that they allow for a broad approach to the problem of carbohydrate cataracts. Information which has been obtained with one type of cataract can be tentatively applied to all types and more freedom is gained in the designing of experiments.

High carbohydrate levels may produce their effect as the result of an osmotic disturbance¹⁸ or a "toxic" state.¹⁹ If osmotic changes are involved, they should be related to the number of sugar molecules in the blood and independent of the structure of these sugars. This is not true in either respect.

The time required for diabetic-cataract formation is essentially the same whether the

level is 400 or 600 mg. per 100 cc.¹¹ This is a 50-percent change in the number of glucose molecules and one would expect a difference in the time requirement if osmotic effects were paramount.

There is no correlation between the blood sugar levels of galactose, xylose and glucose and their effectiveness in producing cataracts.²⁰ This again is not in keeping with an osmotic mechanism for the molecular weights of glucose and galactose are the same and they should be equally effective when present in the same concentration.

Some type of "toxic" state may, therefore, be responsible for the development of cataracts. The term "toxic," however, is not very definitive and is only satisfactory until a more explicit explanation is available.

It is suggested that the "toxic" condition produced by high carbohydrate levels is a cellular metabolic deficiency.¹ This may be the result of a saturation of cellular absorptive mechanisms by sugars so that other metabolites are lost to the cell.

If this is true and if the sugars are absorbed in preference to the other essential metabolites, then high carbohydrate levels provide a permanent block and the only way to prevent cataracts is to lower the blood level of the offending sugar. Similarly, the only way to determine what metabolite is being denied to the cell is to provide it at a time when the blood-sugar level is normal.

It has been demonstrated that supplements provided in this manner will prevent galactose cataracts. Further experiments will be required to determine the specific nature of the essential metabolite and to discover the exact mechanism by which it is kept out of the cell. Since glucose, galactose, and xylose are absorbed with the aid of different enzymes, it is difficult to see how any one of these sugars could saturate a common enzyme system. In the process of absorption, however, these sugars all require adenosine-triphosphate as a source of energy and phosphate. It may be that this is the limiting factor. There is evidence to indicate that the

supply of cellular adenosinetriphosphate is related to the blood-sugar level, for it is decreased when the blood sugar is elevated in diabetes and returns to normal when the blood sugar is lowered by starvation, a high-fat diet, or insulin.^{21,22}

SUMMARY

It has been shown that galactose and glucose act in a synergistic fashion in the production of cataracts and this has been interpreted as indicating that they produce their effect in a common manner.

Ascorbic acid injected intravenously as dehydroascorbic acid and phosphate added to the drinking fluid failed to delay the development of diabetic cataracts.

Rats placed on a 35-percent galactose diet for four days of each week and starved on

three days of the week developed cataracts in an average of 40 days. Rats on an identical galactose regime but receiving a supplement of normal diet instead of being starved three days each week did not develop cataracts.

This was interpreted as indicating that carbohydrate cataracts were the result of a metabolic deficiency that could be corrected by providing the proper supplement at a time when the cellular absorption mechanisms were not blocked by a high sugar level.

2109 Adelbert Road.

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DISCUSSION

DR. DAVID SHOCH (Chicago): I think Dr. Patterson's paper is most interesting, and it has implications of great import in cataract development generally, not only in that due to carbohydrates.

Our own work has been on irradiation cataract and it becomes quite evident as evidence accumulates that these cataracts are essentially one and the same, and we are often only confused by differences in etiology and clinical classification. Essentially we

are dealing with interruptions in metabolic pathways, possibly a common enzyme system, particularly in the carbohydrate cataract. I definitely agree that there is an overloading mechanism, and we might postulate that one of the enzyme systems in glucose metabolism, for instance, would be overloaded with an excess of glucose. Studying galactose-produced cataract really simplifies the problem.

In examining the simplest accepted formulas for

glucose and galactose, we find they are very much the same. In both cases the first three carbons have the same structure. The difference lies in the fourth carbon where there is a *cis* relationship to carbon-3 in galactose and a *trans* relationship in glucose.

On splitting these substances into trioses the fractions become the same because carbons 3 and 4 become asymmetric and the body should therefore be unable to distinguish between trioses from galactose and trioses from glucose. For this reason we feel that the difficulty arises before the splitting into the two triose molecules. The enzyme responsible for splitting the trioses is the aldolase and we feel that it may be this enzyme that is saturated thus interfering with normal metabolism.

Extending this thought to *d*-xylose again we find carbons 1, 2, and 3 the same but a difference in the rest of the chain and, interestingly enough, cataracts have been produced by administering *d*-xylose. A further example is *l*-arabinose which again has the same configuration on carbons 1, 2, and 3, and only two more carbons in the chain. Cataracts have also been reported following saturation with this pentose.

An interesting point is the finding of Dr. Levine at Michael Reese Hospital that insulin can cause a transfer of these four sugars across cell membranes in the eviscerated animal but it cannot effect such a transfer of *d*-arabinose and *d*-mannose which have a different structure in the first three carbons.

In summary, I agree entirely with Dr. Patterson that there is a metabolic interference in the mechanism of carbohydrate cataract and it is possible that a common enzyme system is involved. We are at present attempting to determine whether the aldolases are the enzymes to be implicated.

DR. PATTERSON: I thank Dr. Shoch for his remarks. We have considered some of the things that he mentions, and, if there had been more time, we would have liked to discuss them.

We have not localized the metabolic defect at the point of action of the enzyme aldolase. If one considers the metabolism of glucose, galactose, and xylose, and keeps in mind the effectiveness of these sugars in producing cataracts, it is difficult to localize the metabolic defect at the enzyme aldolase.

Galactose is phosphorylated by the cell to form galactose-1-phosphate, which is immediately changed to glucose-1-phosphate by the action of waldenase in the presence of uridinediphosphoglucose.

From this point on, the metabolism of galactose is identical with that of glucose, so that any splitting to a three-carbon fragment is the same for both sugars. However, galactose is much more effective in producing cataracts than glucose.

Xylose presumably is converted to some type of keto-xylose, which is then phosphorylated and enters the Meyerhof scheme at a lower level. It is not converted to glucose, but enters at the level of a three-carbon fragment. The metabolism of xylose seems to by-pass aldolase.

The work of Dr. Levin, with respect to insulin, is most interesting, and we are now testing its re-

lationship to the development of cataracts. We have tried arabinose in long-term chronic experiments, and so far have not been able to produce cataracts. Perhaps we have not had a high enough concentration. We are trying to see if it will act synergistically with diabetes. If there is a common mechanism, it presumably should have a synergistic effect.

Actually, the possibility that a lack of insulin may be responsible for a metabolic deficiency at a cellular level has not been ruled out. If there is a limited amount of insulin available to the cell, and if other metabolites compete with sugar for this insulin, then the lowering of the blood sugar, such as results with phlorizin, may permit the absorption of the other metabolites, and thus prevent cataracts. The total amount of insulin available to the body as a whole, however, does not seem to be critical, for cataracts can be prevented by lowering the blood sugar without changing the total amount of insulin available to the animal.

DR. JAMES H. ALLEN (New Orleans): I hate to interrupt this profound biochemical discussion, but I think it would be interesting to point out the clinical significance of this study.

For a number of years men in ophthalmology and in diabetic work have assumed that, in addition to an anomaly of carbohydrate metabolism, there have been other factors involved in producing the ocular manifestations of diabetes. Perhaps that is true in some of the degenerative changes in the retina.

I do not believe this study throws any light on that question. However, I would like to say that it does seem to indicate that the anomalous carbohydrate metabolism is the important factor in the development of diabetic cataract.

Some years ago, in a study of diabetic children, Dr. O'Brien and I, working with the pediatric department of the University of Iowa, were able to demonstrate that adequate control of the blood sugar in those children prevented the development of cataract or stopped the early development of diabetic cataract. I believe that report was received with considerable skepticism, but we have seen additional clinical proof of this and now I believe this basic work further substantiates that clinical report. In other words, the anomaly of carbohydrate metabolism seems to be the primary factor in diabetic cataract.

This work also seems to substantiate the clinical observation that galactose cataract in newborn infants will not only stop but, in most cases, will disappear after galactose is removed from the diet.

DR. DAVID G. COGAN (Boston): Dr. Patterson, does the incidence of these carbohydrate cataracts show the species variation that one does get with such other phosphorylating inhibitors as dinitrophenol, or is this a pan-species effect?

DR. PATTERSON: My work has been confined to one particular species and one particular strain,

because we have wanted to standardize our conditions.

In the case of galactose cataracts, Mitchell demonstrated that the strain of the rat makes a big difference as far as the length of time required for the development of cataracts. Diabetic cataracts have been reported in dogs, rabbits, and rats. They appear to be the same type of cataract as seen in man, and described as the juvenile type. These have been described by Dr. Allen and others working in Iowa, and also by Waite and Beetham in Boston. The juvenile cataracts of man can be controlled with insulin in the same way that the diabetic cataracts of rats may be controlled with insulin.

DR. COGAN: Do you have any evidence that the saturation effect, which one obtains, pertains to the same enzyme system associated with the action of dinitrophenol?

DR. PATTERSON: There is no evidence as far as I know. Dinitrophenol produces its effect by dissociating the production of high-energy phosphate from oxidation. This may or may not be involved in the production of cataracts. Dinitrophenol has been given to animals that were on a galactose diet. It had no effect on the development of cataracts.

DR. ZACHARIAS DISCHE (New York): I would like to refer to these figures on the blackboard.

I think it is characteristic that xylose under any circumstances is much more potent in producing cataract than arabinose. Xylose is related to galactose in its structure. Arabinose is related to glucose.

I don't think anybody tries to work with ribose. It would be too expensive to feed ribose to rats.

These facts would indicate that what matters in the galactose cataract is the *cis* position of hydroxyls of the sugar and that the *cis* position interferes with some systems that require a *trans* position.

As far as the aldolase is concerned, there would be the possibility that the phosphorylated form of

galactose would interfere with the aldolase, because phosphorylated sugars tend to interfere with this enzyme.

While ribose is a natural sugar in the animal cells, xylose is not, and I don't know of any evidence (maybe Dr. Patterson knows) that xylose could be phosphorylated by animal cells in any form, either as ketoxylose or as aldooxylose. I would think the strong effect of the xylose is related to the effect of galactose, and that the *cis* position of hydroxyl-3 and 4 in the sugar interferes with some enzyme system which requires a *trans* position.

The fact that glucose also is able to produce cataract indicates to me that these sugars may interfere with the formation of some compounds which depend on either galactose or glucose, and in this respect we thought of the polysaccharide of the lens capsule, which consists of galactose and glucose.

We are now studying this problem from this point of view as to whether there is an interference in the formation of the polysaccharide of the lens capsule by either galactose or an excess of galactose or excess of glucose.

DR. PATTERSON: I would like to make just one short remark.

We are now testing as many sugars as we can to determine which of these sugars may have a synergistic effect with diabetes in the production of diabetic cataracts. This appears to be an easy method of determining which sugars will produce cataracts, and in this way determining what the essential chemical structure for the production of cataracts may be.

We have considered the possibility that a deficiency in polysaccharides might be responsible for cataract formation. It is interesting to note that in the chondroitin sulfuric acid type of polysaccharide, galactosamine is the constituent that is combined with galacturonic acid.

We have tried administering glucosamine as a supplement with the idea that it might be competing with these sugars for absorption. In our limited trial we were not successful in preventing cataracts.

FURTHER EXPERIMENTAL STUDIES ON SYMPATHETIC OPHTHALMIA*

RAYMOND C. COLLINS, M.D.
East Orange, New Jersey

In a previously reported work,¹ it was shown that by injecting guinea pigs intramuscularly and intraperitoneally with macerated guinea pig uvea and the so-called Freund type adjuvants,^{2,3} that is, aquaphor, mineral oil, and heat-killed tubercle bacilli, lesions were produced in the choroid which histopathologically simulated those of sympathetic ophthalmia as found in human eyes.

About 50 percent of the animals so treated exhibited large areas of infiltration in the choroid, consisting of lymphocytes, round, plasma, and epithelioid cells, and Dalen-Fuchs type nodules; whereas, all of the control animals, given only the same mixture of adjuvants without uveal tissue, had normal eye findings. These findings seemed significant enough to warrant a continuation of this work.

The question had been raised, "Could the uveal tissue be acting as an adjuvant producing more antibodies to the tubercle bacilli resulting in choroidal infiltrations due to the antibody-antigen reactions to these tubercle bacilli rather than to the uveal tissue?" In order to answer this important question, the following experiments were performed.

EXPERIMENTAL STUDIES

A. SERIES WITHOUT TUBERCLE BACILLI

Thirty-four young, healthy guinea pigs were given three intramuscular injections at weekly intervals. Each injection of 0.5 cc. contained 0.2 cc. mineral oil, 0.1 cc. aquaphor, and 0.2 cc. saline suspension of 0.5 of a ground guinea-pig uvea.

*From the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology of the Presbyterian Hospital, New York, New York. Supported in part by the Knapp Fund. Presented in part at the 21st scientific meeting of the Association for Research in Ophthalmology, Chicago, June, 1952.

Three weeks after the last intramuscular injection, they all received 0.5 cc. intraperitoneally containing the same amounts of mineral oil and aquaphor, but three guinea-pig uvea per injection. This is the same quantity and injection schedule previously employed except that here the tubercle bacilli were omitted.

Four months after the first injection, all of the animals were killed. One month prior to killing the animals, each one was given an intradermal skin test of 0.1 cc. of a saline suspension of macerated guinea-pig uvea consisting of 0.9 guinea-pig uvea per test dose.

Five cc. of blood were withdrawn from the heart just before killing the animals. Biopsies of the lung, liver, spleen, and injection site were taken. The eyes were fixed in Bouin's, prepared in celloidin, serial sections made, and stained with hematoxylin and eosin.

Results. Complement fixation tests on the sera showed no circulating complement fixing antibodies to macerated uveal tissue. Biopsies of the spleen showed some phagocytosis of pigment. The liver and lung biopsies were negative. The microscopic sections of the skin test sites showed no more reaction or phagocytosis of pigment than those taken from a similarly treated group of normal animals.

All of the eyes of this series of animals were found to be entirely normal. This was not a surprising finding. If these animals had presented the usual positive findings in the uveal tract, the question would have been answered at this point.

Negative findings, though, were not too significant. Kabat, Wolf, and Bezer⁴ showed that not only was it necessary to include the tubercle bacilli with the adjuvants in order to get acute disseminated encephalomyelitis in

monkeys, but that the tubercle bacilli must be in contact with the antigen.

The explanation of these negative findings when the tubercle bacilli were omitted from the adjuvant mixture may well be as follows: One of the most accepted theories to explain the function of the Freund-type adjuvants is that they function by setting up a reactive tissue wall about the inoculum which localizes the antigenic material at the inoculation site and, through slow continuous absorption, produces hyperimmunization. Also, the large monocyte and epithelioid cell response which is called forth by the adjuvants is believed to be an important factor in increasing the antibody production.

Grossly, when tubercle bacilli are included in the mixture, the injection site is found to be a large firm nodule filled with yellowish or cream-colored exudate. Microscopically, it shows a dense cellular reaction with an intense monocyte and epithelioid cell response (fig. 1). However, without the addition of the tubercle bacilli, the inoculation site was difficult, and sometimes impossible to find grossly.

Microscopically (fig. 2), the site of injection without tubercle bacilli showed a very mild reaction consisting of vacuoles separated by thin connective-tissue trabeculae which contained a few lymphocytes. Normal muscle often separated these thin reaction trabeculae. Thus, it can be seen that there is no great monocyte or epithelioid cell response and if this is necessary for the adjuvants to potentiate the antibody production, it is not surprising to find no reaction resulting from a poor antigen given with this mixture omitting the tubercle bacilli.

B. ADJUVANT POTENTIAL OF UVEAL TISSUE

In order to discover whether or not uveal tissue acted as an adjuvant and increased antibody production the following experiments were performed:

Experiment 1. Two groups of 11 guinea pigs each were given two subcutaneous injections on the same day, consisting of 0.25

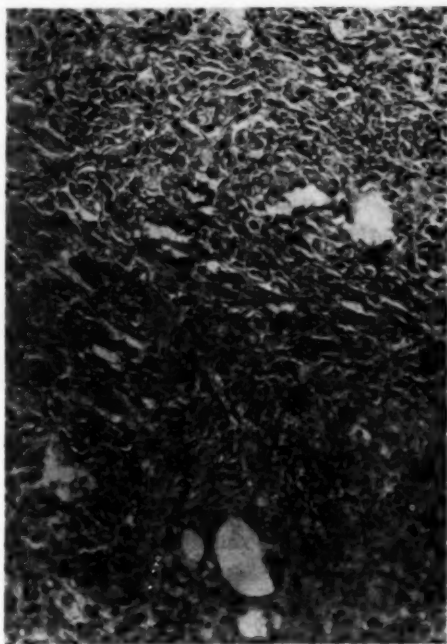


Fig. 1 (Collins). Inoculation site, showing marked cellular response consisting of lymphocytes, numerous monocytes and epithelioid cells, and some giant cells. Mixture contained uveal tissues, mineral oil, aquaphor, and heat-killed tubercle bacilli.

cc. each.^{5,6} In one group of animals, the injections contained heat-killed tubercle bacilli, mineral oil, and aquaphor in the exact same proportions as were used in the previously reported experiments. The injections of the second group contained the same materials except that uveal tissue in the same quantity as previously used was added to the mixture.

At the end of six and one-half weeks, all animals were skin-tested with 0.1 cc. of 1:100 old tuberculin intracutaneously. At the end of 24, 48, and 72 hours, the amount of erythema, swelling, and necrosis was measured and recorded.

Figure 3 shows that there was no significant difference between the skin test reactions of the two groups. If the uveal tissue had acted as an adjuvant in this mixture, one would have expected a more severe

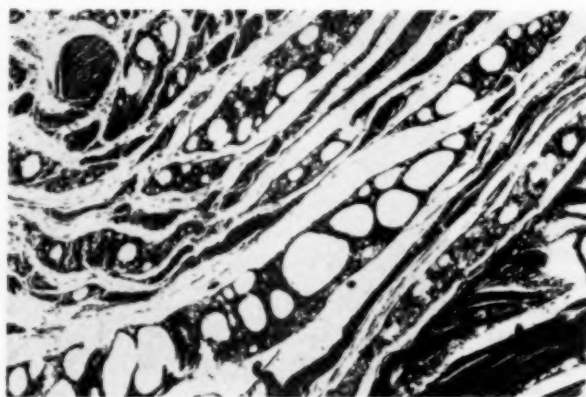


Fig. 2 (Collins). Inoculation site, showing mild reaction consisting of vacuoles, connective-tissue trabeculae, few lymphocytes. Mixture contained uveal tissue, mineral oil, aquaphor, without killed tubercle bacilli.

reaction in the group of animals in which this factor was added to the injection mixture.

At the end of eight weeks, 5.0 cc. of heart's blood was obtained from each animal and a quantitative complement fixation test to tubercle bacilli using the method described by Freund, Laidlaw, and Mansfield (1936)⁷ was performed on each sample of serum obtained from this blood.

Figure 4 shows that there are no more circulating complement fixing antibodies to tubercle bacilli in the group in which the uveal tissue was added to the mixture than in that group wherein it was omitted.

Experiment 2. In order to check the adjuvant powers of uveal tissue by still another

method,⁸ the following experiments were performed:

Two groups of 10 guinea pigs each were given two subcutaneous injections consisting of 0.25 cc. each on the same day. In one group of animals, the injections contained

COMPLEMENT FIXATION TESTS

Tbc + adjuvants

ANIMAL NUMBER	AMOUNT OF SERUM PER TUBE				
	0.2 cc.	0.1 cc.	0.05 cc.	0.025 cc.	0.005 cc.
252	+	+	+	+	+
254	+	+	+	+	+
249	+	+	+	+	+
257	+	+	+	+	+
258	+	+	+	+	+
255	+	+	+	+	+
253	+	+	+	+	+
251	-	-	-	-	-

Tbc + adjuvants + uvea

259	+	+	+	+	-
261	+	+	+	+	-
262	+	+	+	+	-
263	+	+	+	+	-
260	+	+	+	+	-
265	+	+	+	+	-
272	+	+	+	+	-
273	+	+	+	+	-
271	-	-	-	-	-
270	-	-	-	-	-

Normal animals

274	-	-	-	-	-
275	-	-	-	-	-
276	-	-	-	-	-

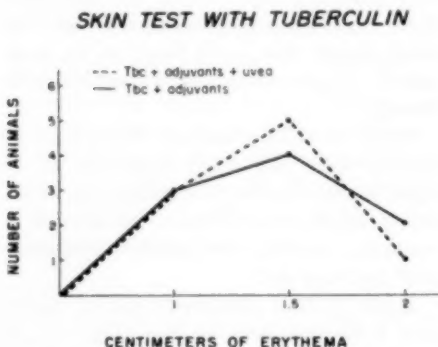


Fig. 3 (Collins). Comparison of skin tests to tuberculin in group of animals given uveal tissue plus adjuvants with group given only adjuvants.

Fig. 4 (Collins). Comparison of complement fixation tests to tubercle bacilli in groups of animals given uvea plus adjuvants with the group given only adjuvants.

heat-killed tubercle bacilli, mineral oil, and aquaphor, plus 0.3 billion killed typhoid bacilli per injection. The second group of animals was given the same injections with a similar mixture to which had been added ground guinea pig uvea.

At the end of eight weeks, 5.0 cc. of blood was withdrawn from the heart of each animal of each group and a macroscopic typhoid agglutination was run on the serum from each blood sample.

Figure 5 shows that there is no higher level of agglutinins to typhoid bacilli in the group with the uveal tissue added to the mixture than in the one wherein this factor was omitted.

C. SERIES WITH MYCOBACTERIUM PHLEI

It has thus far been shown that tubercle bacilli alone with the other adjuvant factors will not cause the choroidal reactions previously demonstrated; nor will uveal tissue plus the mineral oil and aquaphor without the tubercle bacilli. Also, it has been shown that uveal tissue does not increase the production of antibodies to tubercle bacilli, nor does uveal tissue seem to have adjuvant potentials.

Still struggling with the question as to whether or not the tubercle bacilli could be the causative agent in the choroidal reactions which were demonstrated, another series of experiments was performed. It has been amply shown that other substances can be substituted for the tubercle bacilli in this adjuvant mixture.⁹⁻¹¹ In this present work, the timothy-grass bacillus, *Mycobacterium phlei*, a nonpathogen in the true sense of the word, but the producer of a granulomatous type lesion when injected, was substituted for the tubercle bacilli in the mixture.

Seventeen young, healthy guinea pigs were given the usual series of intramuscular injections consisting of 0.5 cc. of a mixture of macerated guinea pig uvea, mineral oil, aquaphor, and heat-killed *phlei* bacilli at weekly intervals for three injections followed by an intraperitoneal injection three

TYPHOID AGGLUTINATIONS

ANIMAL NUMBER	Typhoid + adjuvants					
	DILUTION OF SERUM					
	1:25	1:50	1:100	1:200	1:400	1:800
264	+	+	+	+	+	+
269	+	+	+	+	+	+
268	+	+	+	+	+	+
280	+	+	+	+	+	+
279	+	+	+	+	+	+
278	+	+	+	+	+	+
277	+	+	+	+	+	+
267	+	+	+	+	+	+
266	+	+	+	+	+	+
281	+	+	+	+	+	+

ANIMAL NUMBER	Typhoid + adjuvants + uvea					
	1:25	1:50	1:100	1:200	1:400	1:800
282	+	+	+	+	+	+
292	+	+	+	+	+	+
283	+	+	+	+	+	+
294	+	+	+	+	+	+
290	+	+	+	+	+	+
287	+	+	+	+	+	+
288	+	+	+	+	+	+
289	+	+	+	+	+	+
291	+	+	+	+	+	+
293	+	+	+	+	+	+

ANIMAL NUMBER	Normal animals					
	1:25	1:50	1:100	1:200	1:400	1:800
284	-	-	-	-	-	-
285	-	-	-	-	-	-
286	-	-	-	-	-	-

Fig. 5 (Collins). Comparison of typhoid agglutinations in group of animals given killed typhoid bacilli plus adjuvants with a group given typhoid bacilli, adjuvants, and uveal tissue.

weeks after the last intramuscular one.

Three months after the first injection, the animals were killed. At this time, biopsies were taken of the lung, liver, spleen, and injection site; and the eyes were removed and fixed in Bouin's. Serial sections of the eyes were prepared.

Results. The injection site showed a marked cellular reaction with an extensive outpouring of monocytes and epithelioid cells. The liver and spleen showed phagocytosis of uveal pigment. Seven of the 17 animals (about 42 percent) showed extensive focal areas of infiltration in the choroid of both eyes consisting of round cells, plasma and epithelioid cells, and the majority showed Dalen-Fuchs nodules.

Figure 6 shows a typical choroidal reaction, consisting of round, plasma, and epithelioid cells, and a Dalen-Fuchs like nodule

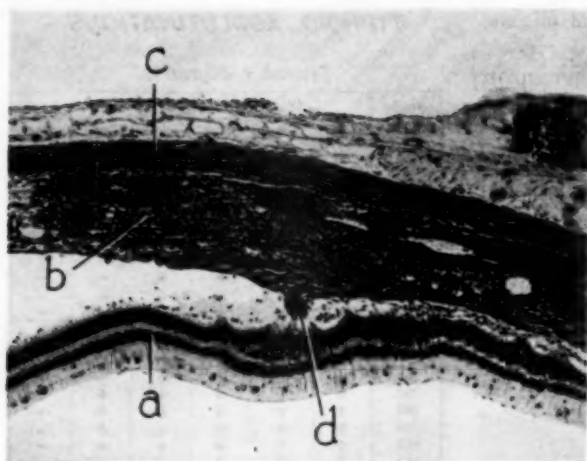


Fig. 6 (Collins). Choroidal reaction seen in right eye of guinea pig injected with a mixture of uveal tissue, mineral oil, aquaphor, and killed phlei bacilli. (a) Retina. (b) Nodule consisting of plasma cells, lymphocytes, and epithelioid cells. (c) Sclera. (d) Dalen-Fuchs nodule.

seen in one of the animals in which *Mycobacterium phlei* was substituted for the tubercle bacilli in the injection mixture. Figure 7 shows an area of choroidal reaction seen in the other eye of this same animal.

D. MONKEY SERIES

In order to extend this work further, it was decided that a series using monkeys as the experimental animal should be done. The serious problem here is one of obtaining adequate monkey uveas to prepare the inoculation mixture. After four months, 33 monkey uveas were collected. In each case, the eyes were removed immediately after death; the uveas were dissected out under aseptic conditions and immediately frozen in dry ice and stored this way.

The mixture was prepared in the usual fashion containing the same amount of mineral oil, aquaphor, and heat-killed tubercle bacilli as previously used, plus 1.6 monkey uveas per cubic centimeter. Four monkeys were given three weekly intramuscular injections of 1.0 cc. of the mixture, followed three weeks later by a fourth such injection.

Twenty-six days after the first injection one of the animals developed a full-blown bilateral iritis with swollen lids, red eyes, photophobia, miosis, and the anterior

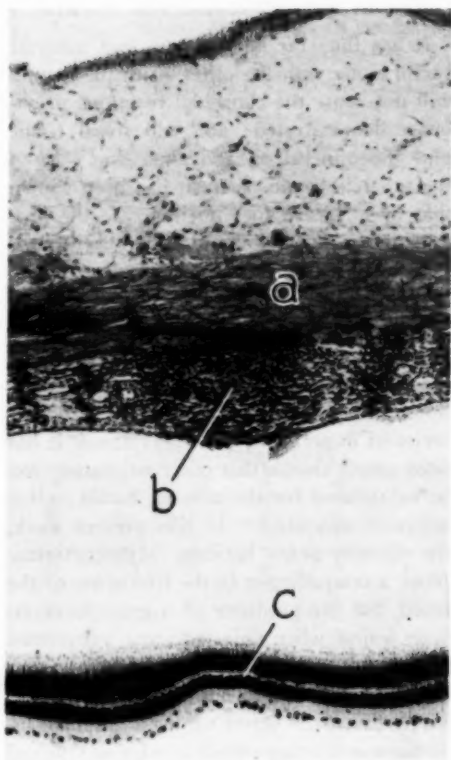


Fig. 7 (Collins). Choroidal reaction seen in left eye of animal shown in Figure 6. (a) Sclera. (b) Choroidal nodule consisting of plasma cells, lymphocytes, and central nest of epithelioid cells. (c) Retina.

chambers filled with cells and fibrin. However, in 10 days, the signs and symptoms subsided, except for a few cells in the anterior chamber.

From two to four months after the first injection, the animals were killed and microscopic sections prepared of the eyes. At the time the animals were killed, they all showed a few cells in the anterior chamber by slit-lamp.

Figure 8 shows an area of round and plasma cell infiltration in the ciliary body of one of the treated monkeys. Figure 9 shows another such area in the choroid of one of these animals. Figure 10 shows a posterior corneal deposit consisting of monocytes filled with pigment granules found in one of the treated monkeys.

E. TRAUMA SERIES

The allergy theory of sympathetic ophthalmia holds that it is an allergy to uveal pig-

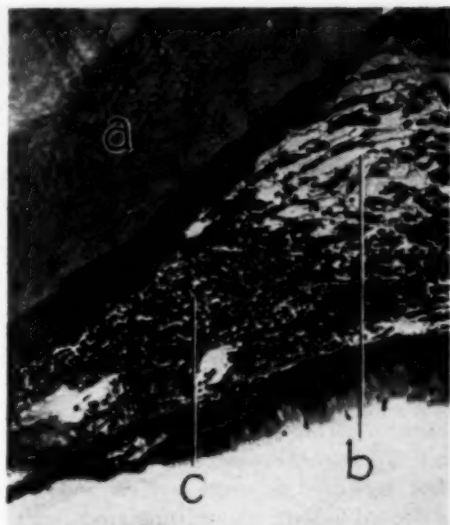


Fig. 8 (Collins). Area of cellular reaction in ciliary body of treated monkey. (a) Sclera. (b) Ciliary body. (c) Cellular infiltration with lymphocytes and plasma cells.

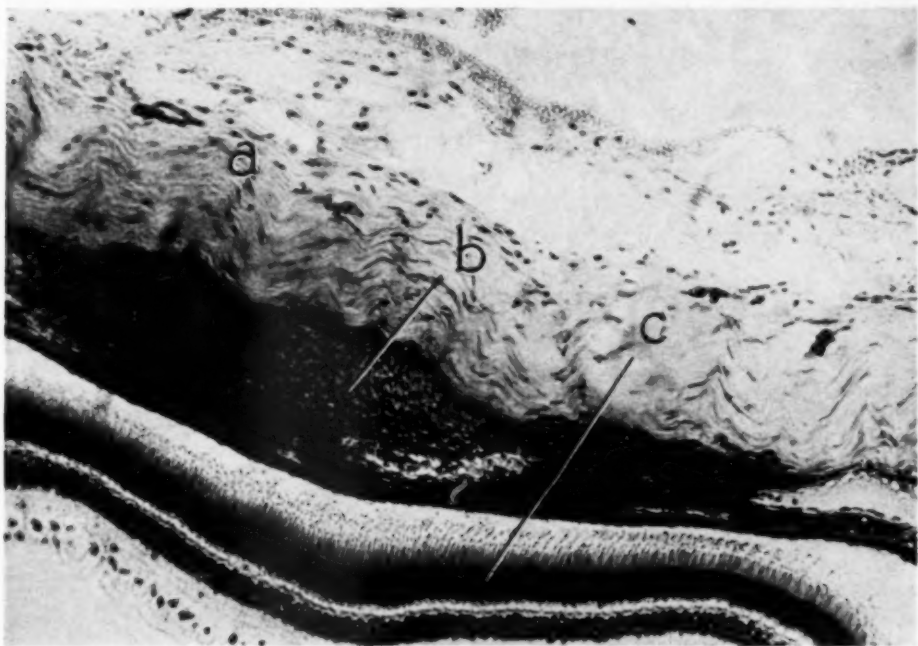


Fig. 9 (Collins). Area of cellular infiltration in choroid of treated monkey. (a) Sclera. (b) Group of lymphocytes and plasma cells. (c) Retina.

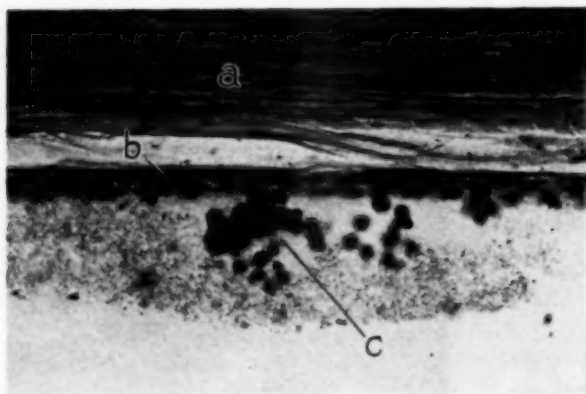


Fig 10 (Collins). Posterior corneal deposit of treated monkey. (a) Corneal stroma. (b) Corneal endothelium. (c) Clump of monocytes filled with pigment.

ment.^{12,13} This pigment is normally intracellular. It was reasoned that if animals were first sensitized to uveal pigment and then subjected to some traumatizing procedure to one of the eyes, this would release the pigment from its protective covering of the cell and a violent local allergic reaction would

result. Thus, 29 young, healthy guinea pigs were given the usual series of injections of uveal tissue plus adjuvants.

From 63 to 84 days after the first injection, an iridencleisis was performed on the left eye of each animal and the ciliary body was traumatized with the spatula in the area



Fig. 11 (Collins). Destroyed eye two months following iridencleisis in treated guinea pig. (a) Sclera. (b) Interior of eye.

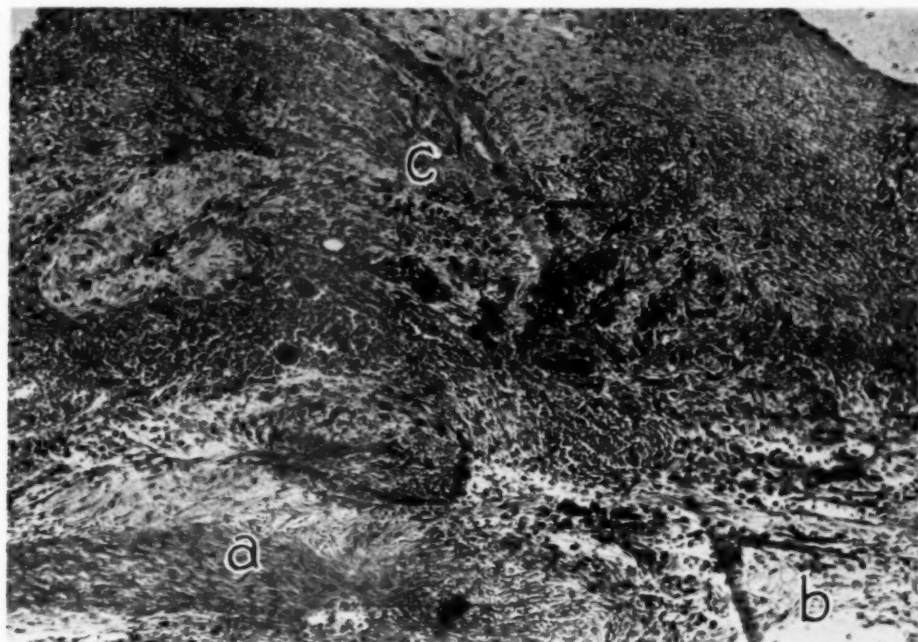


Fig. 12 (Collins). Operation site two months following iridencleisis in treated guinea pig. (a) Sclera. (b) Incision site. (c) Marked reaction, showing giant cells, monocytes, epithelioid cells, lymphocytes, plasma cells, and phagocytosis of pigment.

of the operative coloboma. A similar such procedure was carried out on 16 normal animals—every third animal operated on was a normal control.

Twelve of the 29 operated animals showed a severe reaction of the operated eye in which the eye became beefy red and the anterior chamber entirely filled with grayish-white material, presumably white cells. Such a reaction developed in from one to six days postoperative and the majority of these eyes went on to perforate. None of the normal operated animals showed any significant reaction of the operated eye and these eyes were all white in less than one week. All of the animals were killed in from a few days to two months after operation and sections made of the eyes.

Figure 11 shows a section of an eye two months after the iridencleisis in a treated animal. This eye displayed a violent reaction

immediately after the operation and went on to perforation. Figure 12 shows the operation site two months postoperative in a treated animal. One sees here a marked cellular reaction consisting of round, plasma, giant, and epithelioid cells, and phagocytosis of pigment. Figure 13 shows the operation site two months postoperative in a normal, untreated, control animal. There is no cellular reaction and the structure of the incarcerated iris pillar appears almost normal.

F. CORTISONE SERIES

Because there have been reports of cases of sympathetic ophthalmia successfully treated with cortisone,¹⁴⁻¹⁶ it was deemed wise to test this substance in this work.

Thirty-seven young, healthy guinea pigs were given the usual series of injections of macerated guinea pig uvea plus the Freund type adjuvants, that is, mineral oil, aquaphor,

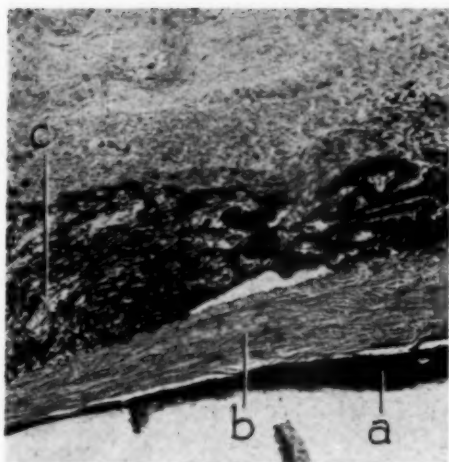


Fig. 13 (Collins). Operation site two months following iridencleisis in normal control animal. (a) Ciliary epithelium. (b) Sclera. (c) Incarcerated iris pillar, showing no cellular reaction.

and heat-killed tubercle bacilli. Starting with the first injection of antigenic mixture, each animal was given 5.0 mg. of cortisone subcutaneously every day except Sundays during the whole course of the experiment.

The animals were followed for five and one-half months, at which time they were killed. The eyes and biopsies of the site of injection, lung, liver, and spleen were taken and prepared for microscopic examination.

Results. The biopsies of the site of injection, liver, and spleen showed a cellular reaction and phagocytosis of pigment similar to that seen in the treated animals without cortisone.

Thirty-three of the 37 animals (about 90 percent) showed extensive areas of choroidal infiltration in both eyes, consisting of round, plasma, and epithelioid cells, and the majority showed Dalen-Fuchs type nodules.

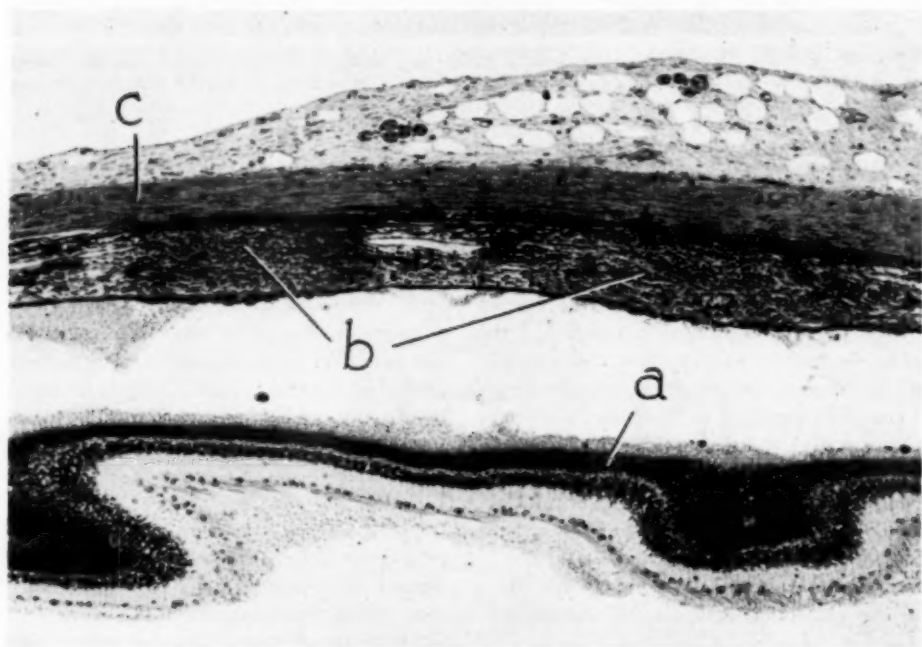


Fig. 14 (Collins). Choroidal reaction in right eye of guinea pig given injections of uveal tissue, Freund-type adjuvants, and cortisone. (a) Retina with folds and separation (arteriahs). (b) Choroidal nodules, consisting of lymphocytes, plasma cells, and epithelioid cells. (c) Sclera.

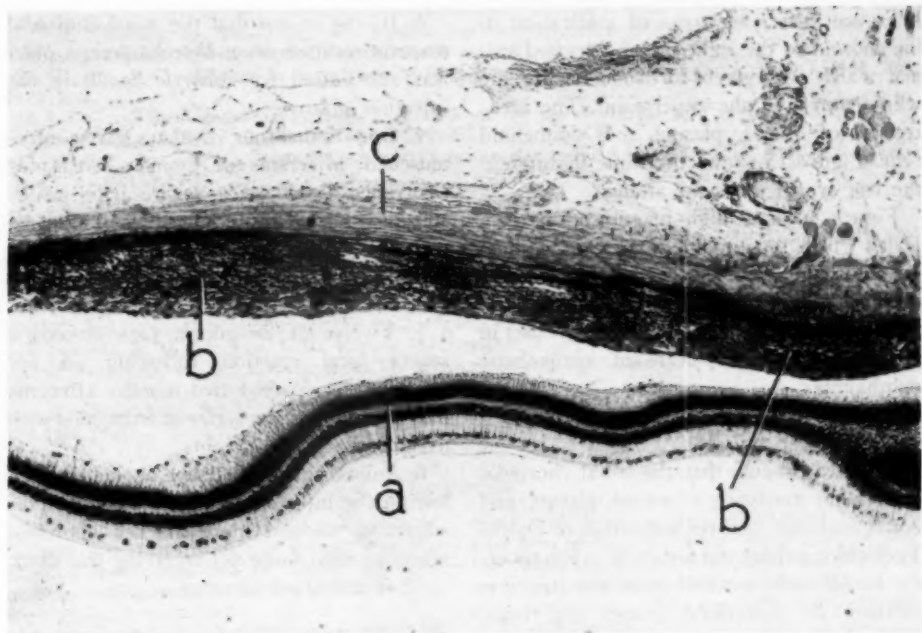


Fig. 15 (Collins). Similar reaction of left eye of same animal shown in Figure 14. (a) Retina. (b) Choroidal nodule. (c) Sclera.

These were the most marked reactions ever seen in any of the series.

Several of the animals showed the whole

choroid thickened and solidly infiltrated—comparable to a Stage III sympathetic ophthalmia seen in human eyes.

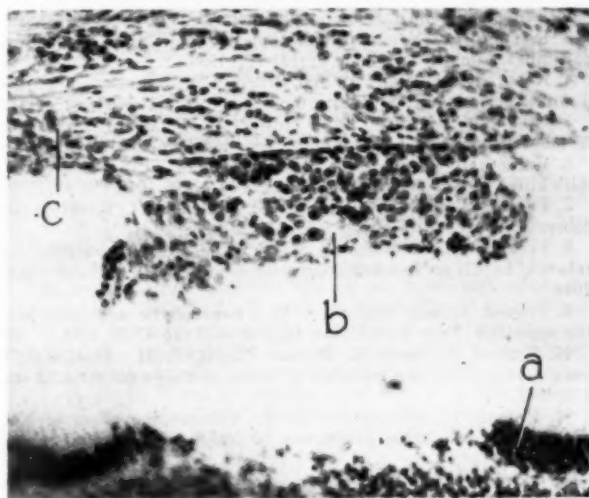


Fig. 16 (Collins). High-power magnification of a Dalen-Fuchs nodule in guinea pig given injections of uveal tissue and Freund-type adjuvant, showing phagocytosis of pigment.

Figure 14 shows areas of infiltration in the choroid of the right eye of a treated animal which was given cortisone during the whole course of the experiment. The areas consist of round, plasma, and epithelioid cells. Figure 15 shows the same findings in the left eye of the same animal.

Figure 16 is a high magnification of a Dalen-Fuchs type nodule in a treated animal which was given cortisone. This shows marked phagocytosis of pigment—a point which Friedenwald²⁰ stresses as important in the histopathologic picture of sympathetic ophthalmia.

SUMMARY

1. It was shown that the usual choroidal infiltration consisting of round, plasma, and epithelioid cells, and the formation of Dalen-Fuchs like nodules did not occur when tubercle bacilli were omitted from the injection mixture of macerated guinea pig uvea, mineral oil, and aquaphor.

2. It was shown that uveal tissues does not have any significant adjuvant potential.

3. It was shown that the usual choroidal reaction resulted when *Mycobacterium phlei* was substituted for tubercle bacilli in the injection mixture.

4. One of the four monkeys given intramuscular injections of monkey uvea plus adjuvants developed a severe iritis which subsided, but all four showed small areas of round and plasma cell infiltration in the choroid or ciliary body on microscopic section.

5. Twelve of 29 guinea pigs showed a severe local reaction following an iridencleisis performed two months after the first injection of the series of injections with uveal tissue plus adjuvants.

6. Animals given cortisone during and following the injections with uveal tissue plus adjuvants showed more marked choroidal reactions than those not receiving this drug.

38 Washington Street.

Cortisone used in this work was cortone acetate (Merck) which was supplied through the courtesy of Merck & Co., Rahway, New Jersey.

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DISCUSSION

DR. DAVID G. COGAN (Boston): I was privileged, this past year, to participate in a small way in a group of experiments with Dr. Byron Waksman, somewhat analogous to the present experiments but directed toward another end.

Dr. Waksman had found that giving single injections of dead tubercle bacilli, aquaphor, and portions of spinal rabbit cord to rabbits produced a transverse myelitis and death. Histologically this was a demyelinating process, simulating multiple sclerosis.

Similarly optic nerves of rabbits were injected with aquaphor and dead tubercle bacilli in the hope of producing a retrobulbar neuritis. The experiments failed. One of the rabbits, curiously enough, developed a bilateral iritis of a transient nature—not a severe case—but no clinically obvious retrobulbar neuritis.

We also made a few spot tests with uvea, aquaphor, and tubercle bacilli and, in the very few experiments we tried, we didn't induce a uveitis.

I would, however, accept Dr. Collins' careful observations in preference to our own, which were just for our own curiosity and were sort of spot tests.

DR. T. E. SANDERS (Saint Louis): I want to ask Dr. Collins about the possibility of the adjuvants changing the antigenicity of the uveal pigment. I have always felt that in production of sympathetic uveitis (and, incidentally, I think uveitis is a better term than ophthalmia), an X factor was added to the uveal pigment which modified the antigenicity.

I wonder if the possibility of the production of these lesions, which surely look like sympathetic uveitis, was due to this factor rather than to changing the absorption of the uveal pigment.

DR. RAYMOND C. COLLINS (East Orange, New Jersey): In relation to Dr. Cogan's work, Kabat,

Wolf, and Bezer, at the Neurological Institute, have been working for six or seven years on this acute encephalomyelitis in monkeys, and they routinely find encephalomyelitis when the monkeys are given brain tissue. They also have found changes in the optic nerves.

Concerning the adjuvants changing the chemistry of the pigment, I cannot answer that question because the chemistry of pigment is so confused. We do not even know about its solubility, let alone alterations in its antigenicity.

As far as getting pure pigment and trying it is concerned, it seems impossible at the present time. The only thing I can say is that this pigment seems to be a relatively inert thing, and when it is injected with this mixture it is picked up and carried around by the reticuloendothelial system. You can find the Kupfer cells in the liver perfectly outlined by pigment granules months later, which microscopically look the same as the granules that were injected. We cannot tell about the chemistry. I cannot answer that.

DR. SANDERS: Melanin might be more than one thing in the uveal tissue. Apparently pure uveal tissue and pure melanin are not antigenic. You must do something to make them so.

DR. COLLINS: We do not know about that. Elschnig's early work showed that uveal pigment had antigenic properties. As far as pure uveal melanin and pure uveal tissue being antigenic, one cannot say with our present state of knowledge.

First, as already mentioned, it is impossible to obtain pure uveal pigment with proven unchanged chemistry and antigenicity. The same holds true of pure uveal tissue.

Secondly, before one could say that pure melanin and pure uveal tissue are not antigenic, one must inject these substances over a very long period. This has never been done. Rivers in the early work

on encephalomyelitis found that he had to inject the brain tissue daily for something like 180 days before he got evidence of antibody production. Kabat found that the adjuvants speeded this reaction to three or four weeks.

DR. SANDERS: That would help to answer my question. It does change the possibility of the antigenicity of it. It increases the antigenicity.

DR. COLLINS: I cannot answer this question any further in view of our lack of knowledge of the chemistry of melanin and exact mode of action of the adjuvants.

DR. LOREN P. GUY (New York): When one is considering the possibility of uveal pigment in sympathetic ophthalmia, I think clinically one should go through the statistics and case reports of sympathetic ophthalmia and find out how many cases of albinos have developed sympathetic ophthalmia. I think that is quite important.

Concerning the specific sensitivity of uveal pigment, it is difficult to test this because it is a matter

of attempting chemically to prepare a pure solution or substance of uveal pigment. You are apt to alter the pigment in attempting this preparation.

Some 10 years or so ago I took guinea pigs and injected them according to the technique of Landsteiner, injecting them every three or four days intradermally. Those guinea pigs did develop an allergy to the pork and bovine uveal pigment that we had. Also, they developed a sensitivity to pork serum and beef serum. This tends to illustrate the complexity of the problem.

DR. RICHEY L. WAUGH, JR. (New Orleans): I was very much interested in Dr. Collins' finding of a nodule in the ciliary body, and I wonder whether or not he found any in the iris, especially since we consider anterior nodules more characteristic of tuberculosis, and those in the posterior iris more characteristic of sympathetic ophthalmia.

DR. COLLINS: Interestingly enough, we found no reaction at all in the iris. It has been localized entirely to the choroid except in monkeys, where there was some action in the ciliary body.

METABOLISM OF FLUID TISSUE CULTURES USED FOR VIRUS STUDIES*

ALSON E. BRALEY, M.D., AND R. C. ALEXANDER, M.S.
Iowa City, Iowa

INTRODUCTION

Fluid tissue cultures have been used to isolate the viruses for a number of years. Simms and Sanders¹ showed that by the use of embryonic mouse brain and serum ultrafiltrate it was possible to maintain the growth of some of the viruses.

A number of problems have presented themselves in the growing of viruses in fluid tissue culture. The viruses certainly increase in concentration when grown in the fluid tissue culture, since there is an increase in virus titer with time. Herpes simplex, for example, will increase to 10^{-3} when grown in this fluid tissue culture.

The virus grows until an apparent equilibrium is reached, at which time there is no further increase in the concentration of the

virus. This would indicate that the cells composing the tissue culture remain dormant and do not increase in numbers, but that the virus increases until it occupies the susceptible cells in the tissue culture.

We wished to determine if the tissue culture is a dormant culture or if the cells in the tissue culture are actively growing. We also wished to determine whether changes in the substrate would change the growth rate or the dormant state of the cultures.

MATERIAL FOR STUDY

Fluid tissue cultures were prepared in a manner similar to that described by Simms and Sanders.¹ Two types of tissue were used in finely divided particles. After the tissue cultures were made, they were placed in centrifuge tubes and spun at a low rate of speed to settle the tissue at the bottom of the test tubes.

* From the Department of Ophthalmology, College of Medicine, State University of Iowa.

The amount of tissue present in these cultures ranged from 1.0 to 1.5 gm., as measured by volume. This was combined with 10 cc. of the fluid substrate and placed in the test cups of the Warburg manometer. KOH was added to the central well of the manometer cups to remove the carbon dioxide.

The manometer cups were then placed in a constant temperature bath maintained at 37°C. These cups were then shaken in the usual manner in the Warburg apparatus, and the readings were made on the manometers at 20-minute intervals for 140 minutes in most instances. The two-or-more-day tissue cultures were allowed to grow in a large volume of fluid for the period of time prior to their being placed in the manometer tubes. These tissue cultures were kept in the incubator, tightly stoppered.

METABOLISM OF NORMAL TISSUE CULTURE

As the oxygen is being removed from the closed circuit of the manometer, it is recorded in millimeters on the manometers.

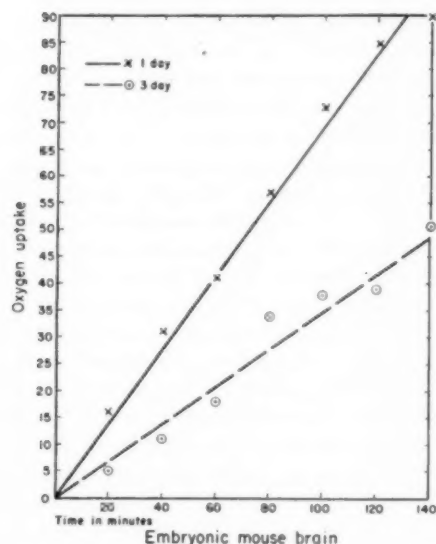


Fig. 1 (Braley and Alexander). Oxygen uptake in embryonic mouse brain tissue culture.

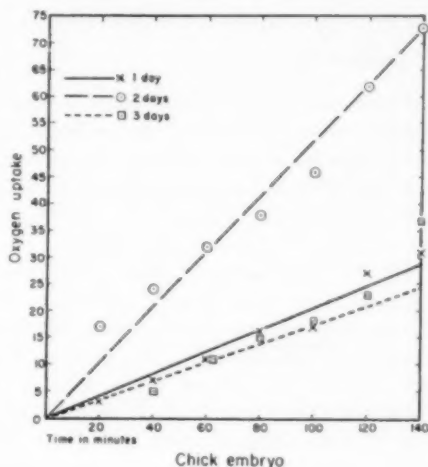


Fig. 2 (Braley and Alexander). Oxygen uptake in chick embryo tissue culture.

Since the carbon dioxide is presumably being removed by the KOH in the well of the manometer cups, it is assumed that oxygen is being consumed in the tissue culture.

In each experiment the fluid portion of the tissue culture, without any cells, was placed in one manometer and used as a control. The excursions of this control manometer, either positive or negative, were recorded as barometric pressure changes and slight temperature changes in the water bath. Invariably this control manometer did not show any excursion, while those containing the tissue absorbed oxygen.

When embryonic mouse brain was used as the tissue, the freshly made, one-day-old tissue cultures showed the greatest excursion. As the tissue cultures were allowed to remain in the incubator for longer periods, the amount of oxygen consumed in the manometers decreased gradually (fig. 1).

Using chick embryo material as the tissue, the two-day-old cultures showed the greatest excursion. The one-day-old tissue cultures showed less excursion on the average, as did the three-, four-, and five-day-old tissue cultures (fig. 2).

SUBSTANCES ADDED TO TISSUE CULTURE

1. HERPES VIRUS

When the herpes virus is added to tissue culture, either embryonic mouse brain or chick embryo, during the first day there is a definite rate of oxygen consumption. This rate is about half the rate of the oxygen consumption of normal tissue culture.

On the second day the rate is increased over the first day, showing a rise in the oxygen consumption during the second day of growth of the herpes virus. This coincides with the marked increase in the potency of the herpes virus when it is tested by intracerebral inoculation in mice. While one-day tissue cultures contain very little herpes virus, the two-day concentration of herpes virus is much higher.

When the three-, four-, and five-day cultures are measured with the herpes virus, it is found that there is a gradual but considerable decrease in the consumption of oxygen by the culture, so that by the fifth day very little oxygen is consumed, yet the potency of the virus when tested in mice is usually 10^{-3} (fig. 3). This observation is based on more than

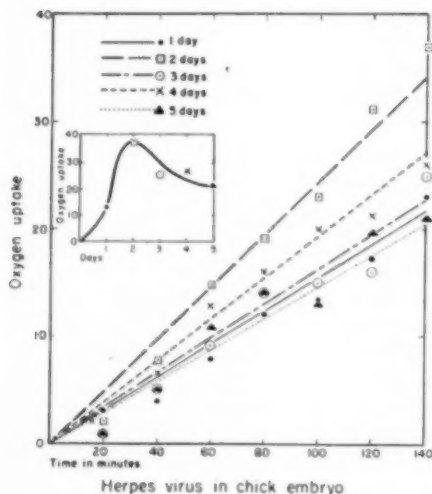


Fig. 3 (Braley and Alexander). Oxygen uptake in herpes virus in chick embryo.

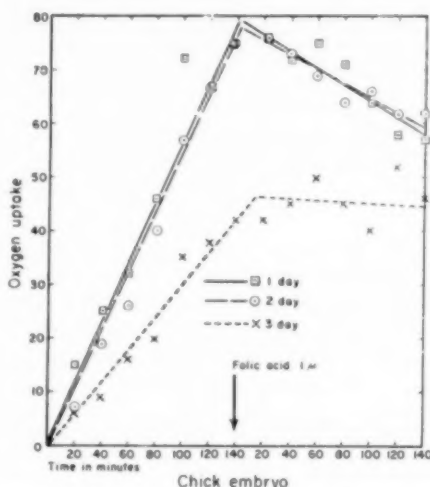


Fig. 4-A (Braley and Alexander). Folic acid in chick embryo tissue culture.

100 tissue culture experiments in each instance.

2. FOLIC ACID

Folic acid was added to the tissue culture by two methods:

(a) At a given moment varying concentrations of folic acid were dumped into the tissue culture so that the resultant concentration of folic acid varied from 1.0 gamma per 10 cc. to 1.0 gamma per 1.0 cc. The oxygen consumption of the normal tissue culture was measured for 140 minutes. A definite curve was thus established. At this time the folic acid was added and the manometer read for another 140 minutes.

In all instances after folic acid was added to the tissue culture, there was an immediate suspension of oxygen consumption, and although the manometer remained steady, as one can see from Figure 4, there was usually a gradual decline in the manometer reading, either due to the loss of the seal around the edges of the manometer or due to the weight of the fluid used for measuring in the manometer. In all instances, however, there was no increase in oxygen consumption.

(b) When folic acid is added to tissue

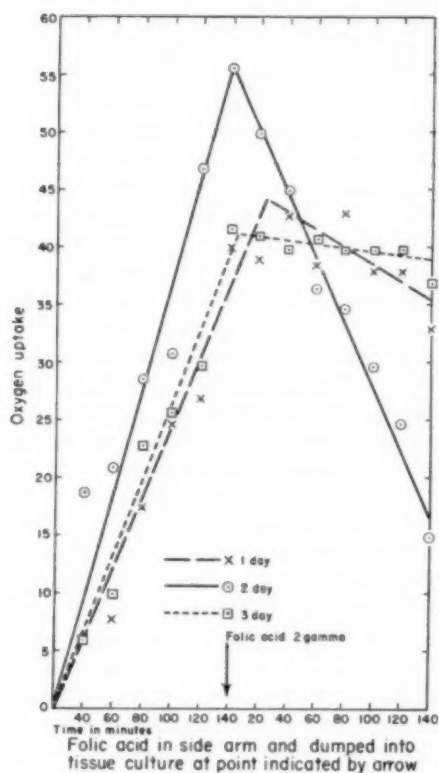


Fig. 4-B (Braley and Alexander). Folic acid in side arm and dumped into tissue culture at point indicated by arrow.

culture in extremely low concentrations of 0.1 gamma to 30 cc., there is not as much

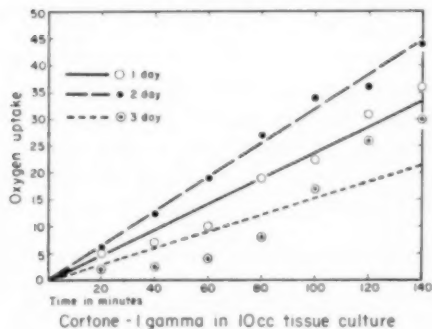


Fig. 5 (Braley and Alexander). Cortone, 1.0 gamma, in 10 cc. of tissue culture.

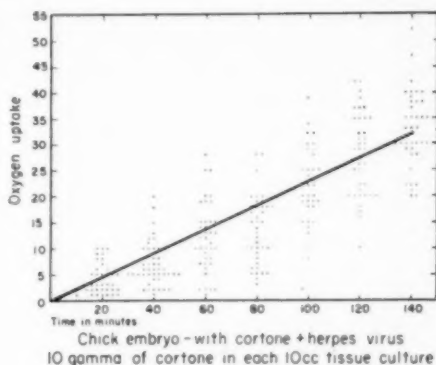


Fig. 6 (Braley and Alexander). Two-day chick embryo, with cortone and herpes virus; 10 gamma of cortone in each 10 cc. tissue culture.

depression of the oxygen consumption. The amount of folic acid added to the tissue culture appears to act as a proportional poison to the tissue. When a large amount of tissue is present in the culture, then larger quantities of folic acid must be added.

(c) When both folic acid, in extremely small concentrations, and herpes virus are added to tissue culture, there is a marked depression in the rate of oxygen consumption, and as has been reported before,² there is no growth of the herpes virus.

3. CORTISONE

(a) Cortisone in various concentrations. Two and one-half percent cortisone was mixed with large quantities of balanced salt solution. In concentrations below 10 gamma per cc., cortisone appears to be in solution since there is no visible evidence of any precipitated material. When cortisone is added to normal tissue culture in concentrations of from 0.1 gamma to 10 gamma per cc., there is no difference between the oxygen consumption by this method and the normal.

There was, however, as can be seen in Figure 6, a marked difference in all manometer readings. While some of them did show a marked increase over the normal oxygen consumption, others showed a definite decrease from the normal. For that

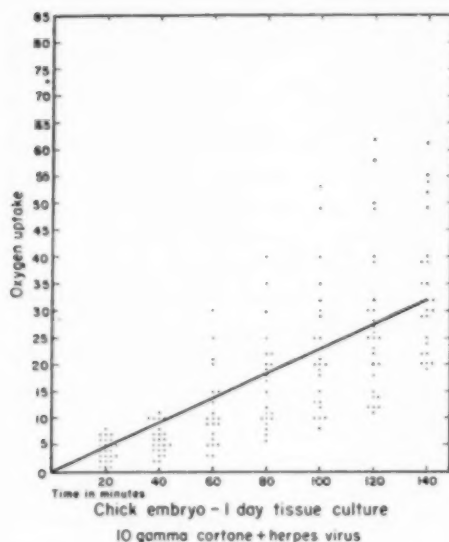


Fig. 7 (Braley and Alexander). One-day chick embryo tissue culture; 10 gamma cortisone and herpes virus.

reason all the points are plotted on Figure 6. This was true not only for 1.0 gamma but for 10 gamma per cc. of cortisone.

(b) Cortisone and herpes virus. Cortisone added to the tissue culture and then inoculated with herpes virus does not show any change in the oxygen consumption from that of the normal tissue culture and herpes virus. The same type of curve is obtained (fig. 7) with herpes virus alone as with the tissue culture.

When this tissue culture with cortisone and herpes simplex is tested in mice, there is very little difference between the potency that is developed between it and controls, as will be seen in Figure 8. Cortisone in tissue culture without herpes virus, grown for the same period of time, produces no effect when inoculated intracerebrally in mice.

DISCUSSION OF RESULTS

From the experiments on normal tissue culture it would seem to indicate that with embryonic mouse brain there is possibly some growth of some of the cells in tissue

culture during the first 24 hours. However, after this period the respiration rate is approximately that of a dormant cell and, therefore, we would consider that the normal embryonic mouse brain tissue culture is a dormant culture and not an actively growing tissue culture.

It would appear that the best time to inoculate these cultures with viruses would be during the first 24 hours. However, no difference appears to result in the final potency of herpes simplex virus whether the tissue culture is inoculated on the first day or the fourth. After the fifth day, when there is very little oxygen consumption by the normal tissue culture, there is likewise very little increase in potency of the herpes virus.

With chick embryo material the most active period appears to be the second day after the tissue culture is made. Therefore, it would seem to be advisable to inoculate the second-day tissue culture with the viruses in order to get the highest degree of potency. This is certainly true of the strain of herpes simplex virus with which we were dealing, although as long as the tissue culture is inoculated during the first three days after having been incubated, it will attain a potency of 10^{-8} within 48 to 72 hours.

When tissue culture is inoculated with herpes simplex, there is an immediate depression in oxygen consumption, which is followed in 24 hours by a slight rise in oxygen consumption. This slight rise is present for the second 24-hour period. Then the

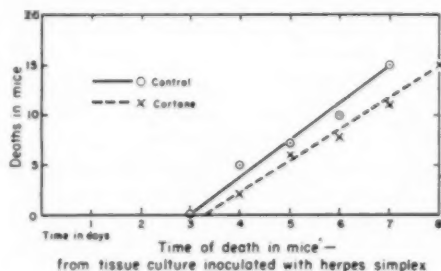


Fig. 8 (Braley and Alexander). Time of death in mice. Tissue culture inoculated with herpes simplex.

third, fourth, and fifth days show a gradual decline in oxygen consumption until the highest potency of the virus is attained, at which time there is no oxygen consumption.

It would appear that both the cells and the herpes virus are then in a dormant state. However, the potency of the herpes virus, when tested in mice, is maintained for a considerable period of time, but with our herpes simplex virus we have never been able to get higher than 10^{-3} concentration.

If our experience with herpes simplex virus and tissue culture can be carried over into the isolation of virus by the use of tissue culture, then it would indicate that freshly made 24 to 48 hour tissue culture should be inoculated with the material in which a virus is suspected. These should be either transferred to other tissue culture or tested by intracerebral inoculation in mice before the fifth day of growth in the incubator. It would be preferable to inoculate or transfer to another tissue culture within 24 to 72 hours after inoculation.

When folic acid is added to the tissue culture in extremely low concentration, then there is only a slight depressive effect. However, it appears from our experiments that the amount of folic acid needed is directly proportional to the amount of tissue present in the cultures. When small amounts of tissue are present in the cultures, then smaller amounts of folic acid are necessary to stop the respiration. However, when large amounts of tissue are present, then smaller amounts of folic acid only depress the oxygen consumption.

In either instance when folic acid is added to tissue culture in almost any concentration, the herpes virus will not grow. In a previous report,² we have indicated that folic acid must combine with the nucleus of the

cells in the tissue culture, thus preventing the growth of herpes virus.

The results of the cortisone experiments would indicate that cortisone has no effect on the tissue culture or on the growth of the herpes virus. The tissue culture to which cortisone has been added acts very much like the normal tissue culture, with the exception that it is likely to be more erratic in the amount of oxygen consumption since some cultures are slightly depressed and others increase very rapidly in the amount of oxygen consumption. When herpes simplex virus is inoculated into tissue culture containing cortisone, there is no increase in the potency of the herpes virus and there is no change in the rate at which the virus develops.

CONCLUSIONS

1. Fluid tissue cultures used for isolation of viruses contain dormant cells.
2. Embryonic mouse brain cultures should be inoculated with virus during the first 48 hours after preparation.
3. Chick embryo cultures should be inoculated within 72 hours.
4. Virus cultures should be transferred or tested in mice 48 to 72 hours after inoculation with viruses.
5. Folic acid added to tissue culture depresses the oxygen consumption in proportion to the number of cells present. It combines with the nucleus and prevents cellular metabolism. Folic acid inhibits or prevents the growth of herpes virus in tissue culture.
6. Cortisone added to tissue culture has no effect on the oxygen consumption of the culture.
7. Cortisone has no effect on the growth of herpes simplex virus in tissue culture.

University Hospitals.

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DISCUSSION

DR. DAVID G. COGAN (Boston): Do I see any grounds of conflict between what you find as the effects of cortisone on tissue culture, and what the California group presented yesterday, indicating that cortisone enhanced the virulence of viruses?

DR. BRALEY: I said that, as far as I was concerned, it had very little effect on the rapidity of growth of the virus. I had hoped it would increase the rapidity with which the virus would increase in concentration.

DR. V. EVERETT KINSEY (Detroit): I would like to ask Dr. Braley what the rationale was for using cortisone.

DR. BRALEY: It was on the basis of clinical evidence—using it in herpes during the first few days of an active herpes infection. Clinically there is no doubt that the virus spreads over the cornea during the first few days.

After the disease has more or less passed on beyond this first few-day period, cortisone may be somewhat beneficial in the prevention of the disc form, and so on, but certainly it appeared clinically to increase the potency of the herpes virus on the cornea—at least the spread of the virus on the cornea.

DR. KINSEY: You would expect that to be systematic, however, would you not?

DR. BRALEY: I expected it also to be true in our tissue cultures, that we would have a sharp rise in the virus concentration. Instead of having to wait three days to reach a 10^{-8} potency, we would get it in one day with the cortisone, you see.

DR. DAVID G. COGAN (Boston): May I intersperse a remark that may be of general interest, although it does not bear directly on Dr. Braley's paper? It pertains to the question: What is happening during the first three days, called the latent period, after the inoculation? Dr. Henry F. Allen, in Boston, studied this and published a paper, but not in the ophthalmic journals, therefore some of you may not know about it.

Dr. Allen was interested in the effect of gamma globulin on the inhibition of the herpes virus when injected intraperitoneally in mice at intervals after an intracerebral injection of the virus. He found that it was completely inhibitory within the first two days after the inoculation, slightly inhibitory on the third day, and not at all on the fourth day.

The reason, presumably, is that the virus is extracellular in the first two days. Sometime thereafter, at least in the case of the mouse brain, it becomes intracellular and is no longer available for the action of the gamma globulin, assuming that gamma globulin cannot penetrate into the cell.

The incubation period of herpetic keratitis in the cornea is also three or four days. Presumably the failure of gamma globulin and other agents which would be specific for it is that they just don't get into the cell where the virus is at this stage.

EXPERIMENTAL STUDY OF PLASTIC MATERIAL AS REPLACEMENT FOR THE CORNEA*

A PRELIMINARY REPORT

WILLIAM STONE, JR., M.D. AND ELIZABETH HERBERT

Boston, Massachusetts

This work was initiated at the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital in an attempt to develop a procedure which might be complementary to the living-donor corneal transplantation and which might possibly be of aid when this procedure yields unfavorable results.

* From the Massachusetts Eye and Ear Infirmary and the Massachusetts General Hospital. This work was supported in part by the Office of Naval Research, Nonr469(00)—NR 115-163 and by the National Society for the Prevention of Blindness.

The greatest percentage of failures in living-donor corneal transplantation, according to Stansbury,¹ and to the symposium on corneal transplantation presented before the American Academy of Ophthalmology in 1947,² is due to clouding of the donor graft and ingrowth of vessels. It would seem desirable, therefore, to attempt to develop an artificial graft into which vessels could not grow and which could not cloud.

Several unsuccessful attempts to replace living corneal tissue with an artificial material have been recorded.³⁻⁸ Stimulation was

given to try like procedures by an observation made during the war. Coming under observation were several pilots of dive bombers whose plastic cockpit cupolas had collapsed and shattered into thousands of minute pieces, many of which were imbedded in their corneas. In several cases, the particles were so small and so numerous that removing all of them would have meant practically removing the entire cornea. They were to a great extent, therefore, left in place. Peculiarly enough they produced very little, if any, reaction.

As a result of this observation, it was thought that it might be interesting to determine how the cornea would tolerate larger pieces of plastic.

FULL-THICKNESS PLASTIC REPLACEMENTS (1947)

Plastic replacements of various shapes and sizes were placed in 15 rabbits as full-thickness grafts five years ago. All of these grafts extruded within a 14-day period.

Several had tantalum meshwork at the edge, others were merely buttons, others had roughened edges (fig. 1). We did not know at that time that there is a correlation between the interstice size of tantalum mesh and tissue ingrowth.⁹

All the plastic discs were round in shape and were sutured in place by means of the classical silk suture method. In all rabbits, adequate antibiotic therapy was administered.

INTERLAMELLAR MOLDED IMPLANTS

Two years ago a different principle was explored. It was decided to attempt to apply a principle which had been demonstrated with the incompletely covered plastic mesh postnucleation implant—that is, that it is necessary to keep tissues in apposition to the mesh with suitable suture material a sufficiently long period to allow the tissues to grow firmly into the interstices of the meshwork.⁹

If the plastic could be maintained in the



Fig. 1 (Stone). Some of the plastic discs placed five years ago as full-thickness implants in rabbit corneas. All extruded within a period of one to two weeks.

cornea sufficiently long for tissue to grow firmly into its periphery, and if the periphery were fabricated to permit the ingrowth of tissue, it might be maintained without extrusion. A two-stage procedure for the corneal implant was therefore devised.

The implant first used was one made of annealed methyl methacrylate, machined to the size and shape of the rabbit's cornea, with holes of different diameters in the periphery to allow for tissue ingrowth (fig. 2). These were placed in one eye of nine rabbits two years ago.

The operative procedure consisted in incising the cornea at the limbus, splitting the cornea in two layers from limbus to limbus, sliding the implant between the two layers, and then suturing the cornea in the periphery.

The plastic was well tolerated in all the diameters and thicknesses used. Even in the first seven days there was little reaction in the cornea, either of infiltration or desquamation (fig. 3).

Several days later several small vessels began to form in the eyes of four rabbits. In one rabbit, five small vessels branched out from the limbus; in another rabbit, after several weeks, the vessels began to regress to some

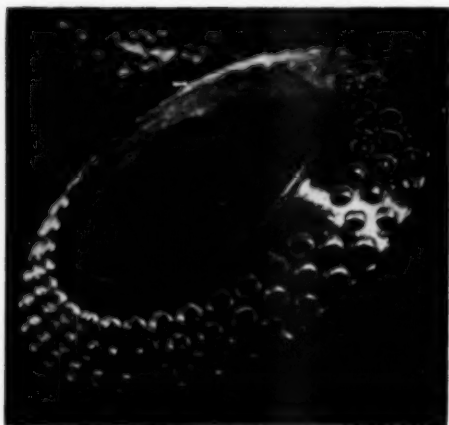


Fig. 2 (Stone). Type of corneal disc placed in rabbit corneas two years ago. At present, experiments are being conducted with a completely different design.

degree until they became very fine lines (figs. 4 and 5). They exist now as two to three trunks from the periphery to the area of the holes and then arborize in fine filaments into

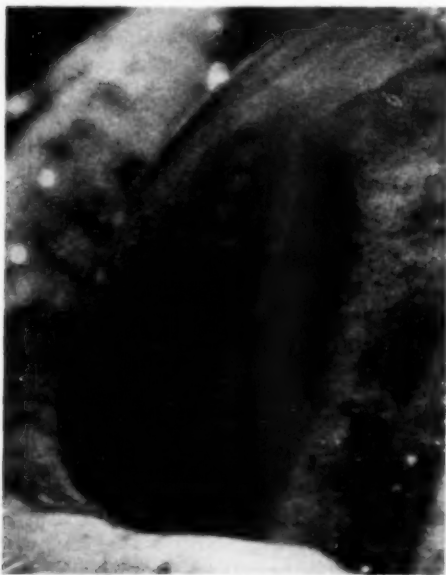


Fig. 3 (Stone). Interlamellar implant in rabbit cornea, seven days postoperative. Very little reaction in cornea or remainder of eye.

the holes. They invaded the central area of the plastic corneas but later regressed completely, leaving little vestige.

An explanation of the cause of this moderate but apparent vascularization may be found in the type of polishing material used and its accumulation in the peripheral holes. It may also be due to the proximity to the limbus of our original incision. These questions are being investigated at present.

The photographs (fig. 4 and 5) were taken five months after plastic discs were placed in rabbit corneas. These discs are still in place at the end of 24 months and are essentially unchanged (fig. 6).

Rabbit 95 died seven months after the implant was placed. In teasing the implant from between the corneal layers, it was found that the stroma had grown firmly into each of the holes and it was very difficult to separate the implant from the surrounding tissue in the region of the holes. (fig. 7).

Late extrusion. Two interlamellar discs placed in this series extruded at the end of 19 months. It was felt that this extrusion was



Fig. 4 (Stone). Interlamellar implant in rabbit cornea, five months postoperative. Cornea clear, with exception of several fine blood vessels.

due to gradual erosion of the anterior corneal layer at one edge as a result of pressure between the overriding lid and the implanted plastic. As a result of this, new types of discs, completely different from those shown in Figure 2, have been designed with a view to their protective features. Experiments are being carried on with these at present.

SECOND STAGE IN THE TWO-STAGE PROCEDURE

The first stage, as has been seen, was to devise a method of maintaining an implant in apposition to corneal tissue for a sufficiently long period for firm fibrosis to take place in the periphery.

The second stage consisted in trephining a segment in the center of the anterior layer of cornea, after a sufficient time interval, and, if necessary, according to the opacification, in doing the same to the posterior layer. One part of this second stage occurred inadvertently in Rabbit 85 (fig. 8).

An implant, 0.5-mm. in thickness and 12-mm. in diameter, had been placed. This extended practically from limbus to limbus. When the anterior layer was resutured in

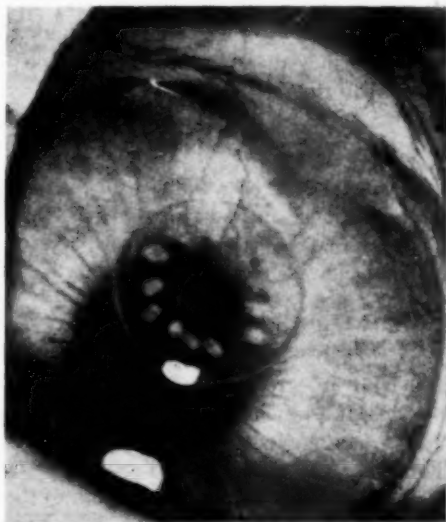


Fig. 5 (Stone). Interlamellar implant in rabbit cornea, five months postoperative.



Fig. 6 (Stone). Interlamellar implant in rabbit cornea, 24 months postoperative. Cornea clear, with exception of several fine blood vessels and a one-mm. area of opacity at edge of implant. Remainder of eye appears normal.

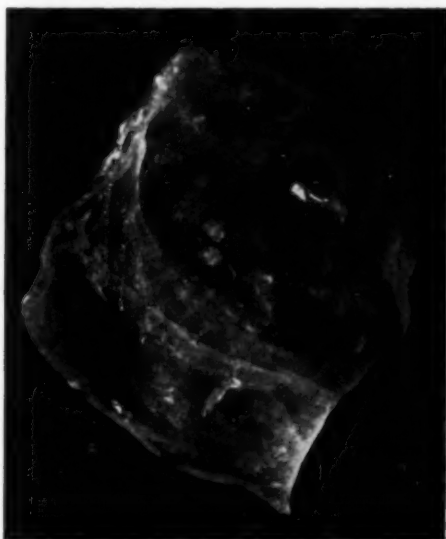


Fig. 7 (Stone). Photograph shows rabbit cornea after interlamellar implant had been teased from it. Projections are corneal tissue which had grown into holes in periphery of implant. (Rabbit 95 died seven months after implant was placed.)

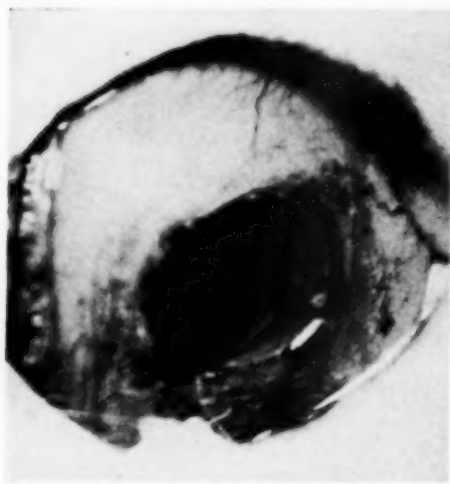


Fig. 8 (Stone). Interlamellar implant in cornea of Rabbit 85, with circular opening in anterior layer of cornea down to plastic. Eye is white and quiet. Anterior chamber can be seen clearly. Photograph taken 12 months postoperative.

the periphery, it was found to be under considerable tension. Consequently, several days later, the stitches pulled out. The anterior layer of cornea retracted leaving a large area of plastic bare of corneal tissue on its anterior surface.

The retracted anterior layer became opacified in a short time, but, aside from this, the eye became white and quiet and the implant did not extrude. A very thin film formed on the anterior layer at one time. This was examined microscopically for cells and none were found. It was found that this film was polished away with ease. The corneal tissue at the edge of the hole remained stationary.

Up to the time of the natural death of this rabbit, 12 months after the disc was placed, the anterior chamber could be seen very clearly through the plastic opening; it was full and the eye showed no reaction.

DISCUSSION

It has been interesting that the cornea could tolerate such large foreign bodies with so little reaction for so long a period of time. It has also been interesting that the incompletely covered foreign body, the disc in the

cornea with the trephine hole in the anterior layer, could have remained without extrusion. Not yet known are the optimal time and method for placing this anterior trephine hole; nor is it known what happens to the corneal epithelial cells. These problems are being investigated.

The problem of the posterior layer is an important one. Work has not, as yet, progressed sufficiently far to report.

In the fabrication of the implants, small details in their preparation and handling cause various reactions in the cornea and influence the success or failure of the procedure. For this reason, it is felt that, at this time, the fabrication of those implants should remain strictly in the hospital laboratory, where every phase in their production can be minutely followed and analyzed, where continued studies can be conducted, and where the chance of overenthusiastic commercial exploitation can be minimized.

Since two implants extruded at the end of 19 months and since animal experimentation is not yet adequate, it is felt that human experimentation is completely unjustified at the present time. Because of the possibility of late complications, it is felt that the monkey, with a longer life expectancy, should be the laboratory animal of choice rather than the rabbit.

CONCLUSION AND SUMMARY

1. A method has been evolved for the fixation of artificial implants in rabbit corneas by means of fabrication of the periphery of the implants to permit firm ingrowth of corneal tissue.

2. Interlamellar plastic implants have been placed in rabbit corneas and are well tolerated with little reaction up to the present, a period of 24 months.

3. An incompletely covered interlamellar disc remained in place in one rabbit cornea for 12 months, up to the natural death of the animal. An operative method has been evolved for producing this incompletely covered implant.

4. Because of late complications in two animals, it has been decided to use the monkey as the experimental animal in the future and to delay human experimentation.

5. Because of the difficulties in fabricating implants and the minute care and inspection

necessary, and to minimize the possibility of overenthusiastic premature commercial exploitation, it is thought best to keep the fabrication of these implants in the hospital laboratory at this time.

243 Charles Street (14).

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DISCUSSION

DR. DAVID G. COGAN (Boston): I would agree with Dr. Stone that it would be desirable to have monkey experiments. I think using the rabbit does fortuitously give one quite a margin of safety, because it is well known that the rabbit cornea will tolerate insults much less readily than do human corneas. Anything that stays in a rabbit cornea certainly will be tolerated by a human cornea.

DR. CONRAD BERENS (New York): May I ask

Dr. Stone whether he has tried this in a dog, and if that would be a suitable animal.

DR. STONE: I have not tried it in a dog, Dr. Berens, and I think a dog most likely would be a suitable experimental animal for this work.

I don't know the exact difference between the cornea in the dog and the cornea in the monkey, but I should think the monkey cornea would be much more akin to the human cornea than the cornea of a dog.

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TWENTY-FIRST MEETING
of the
Association for Research in Ophthalmology, Inc.

Proceedings

Business Session
Auditors' Report

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Geographical List

New Members

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June 10-12, 1952

BUSINESS MEETING

Wednesday Morning, June 11, 1952

The business meeting was called to order at 11:30 A.M., by Dr. David G. Cogan, chairman of the Board of Trustees.

CHAIRMAN COGAN: The first order of business is the report of the secretary-treasurer.

(Report of secretary-treasurer read by Dr. Allen. See auditor's report attached.)

CHAIRMAN COGAN: You have heard the report of the secretary. What is your pleasure?

DR. BRITAIN F. PAYNE: I move the report be accepted.

(The motion was duly seconded, put to a vote, and carried unanimously.)

CHAIRMAN COGAN: May we have the report of the auditor appointed to check this report?

DR. PAYNE: I have found Dr. Allen's report to be correct. I move it be accepted.

(The motion was duly seconded, put to a vote, and carried unanimously.)

CHAIRMAN COGAN: May we have the report of the nominating committee?

DR. T. E. SANDERS: The nominating committee wishes to present the name of Dr. Michael J. Hogan as trustee, and Dr. James H. Allen as secretary-treasurer.

DR. FRANK NEWELL: I move that nomi-

nations close and that Dr. Hogan and Dr. Allen be elected unanimously.

(The motion was duly seconded, put to a vote, and carried unanimously.)

CHAIRMAN COGAN: Dr. Clark, will you give us your report from the trustees?

DR. CLARK: Your trustees, in recognition of meritorious service of some of our elder statesmen, would like to submit the following names for honorary membership: Dr. W. L. Benedict of Rochester, Minnesota; Dr. Eugene Blake, of New Haven, Connecticut; Dr. John N. Evans, Brooklyn, New York; Dr. Frederick Verhoeff, of Boston, Massachusetts.

CHAIRMAN COGAN: We might add that the selection of these names is in some measure an expression of the appreciation we have for the endeavors of these men in the founding and developing of this organization.

DR. SANDERS: I move the election to honorary membership of the men whose names have been submitted.

(The motion was duly seconded, put to a vote, and carried unanimously.)

There being no further business, the meeting was adjourned at 11:55 A.M.

AUDITOR'S REPORT

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

To the Members of the Board of Trustees
Association for Research in Ophthalmology, Inc.
New Orleans, Louisiana

Gentlemen:

SCOPE OF EXAMINATION

We have examined the accounts of the secretary-treasurer of the Association for Research in Ophthalmology, Inc., for the year ended December 31, 1951. In this connection, we have reviewed the system of internal control and the accounting procedures of the association and have examined accounting records and other supporting evidence, by methods and to the extent we deemed appropriate. Our examination was made in accordance with generally accepted auditing standards applicable in the circumstances and included all procedures which we considered necessary.

CERTIFICATE

In our opinion, the accompanying statements present fairly the fund balances of the Association for Research in Ophthalmology, Inc., as of December 31, 1951, and the total receipts and disbursements for the year then ended, in conformity with generally accepted accounting principles relating to the operation of funds, applied on a basis consistent with that of the preceding year.

Yours very truly,
B. B. WOOLLEY & Co.
New Orleans, Louisiana

CASH AND SECURITIES IN FUNDS AS OF DECEMBER 31, 1951

	General Fund	Proctor Medal Fund	Total
Cash in bank	\$1,598.05	\$ 15.37	\$ 1,613.42
Cash on hand	137.00	—	137.00
	<u>\$1,735.05</u>	<u>\$ 15.37</u>	<u>\$ 1,750.42</u>
<i>Securities:</i>			
U. S. Treasury bonds*	—	10,184.63	10,184.63
Total Funds	<u>\$1,735.05</u>	<u>\$10,200.00</u>	<u>\$11,935.05</u>

* At cost, 2½% due 1967-72.

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

Year ended December 31, 1951

		General Fund	Proctor Medal Fund
<i>Cash in Bank</i> —First of Year		\$1,812.44	\$15.37
<i>Add—Receipts:</i>			
1950 dues:			
6 educational members at \$2.00 each	\$ 12.00		
23 active members at \$5.00 each	115.00		
1 sustaining member	10.00*	137.00	
1951 dues (<i>See page 179</i>)		2,975.00	
1952 dues:			
1 educational member at \$2.00	2.00		
1 active member at \$5.00	5.00	7.00	
Banquet proceeds		610.00	
Bond interest		175.00	
Contribution		5.00	
		<u>\$3,909.00</u>	<u>—</u>
Total Receipts		\$5,721.44	\$15.37
<i>Deduct—Disbursements:</i>			
Convention expenses:			
Dinners	806.60		
Programs, mailing fees, notices	284.10		
Expenses of Secretary-Treasurer	250.00	1,340.70	
Stationery, supplies and printing		268.76	
Printing proceedings—1950 meeting		1,023.85	
Auditing		133.00	
Postage		99.00	
Addressograph		51.25	
Insurance—\$5,000.00 position bond—Secretary-Treasurer		25.00	
Safety deposit box rental (1 year)		9.60	
Cash award for best 1950 convention paper		100.00	
Proctor medal		150.56	
Telephone and telegraph		8.57	
Salaries		158.50†	
Contributions		600.00	
Refunds to members for duplicate payments of dues		12.00	
Check returned by bank		2.00	
Bank charges		2.80	
Taxi fare80	
Total Disbursements		<u>3,986.39</u>	<u>—</u>
Receipts over Disbursements		1,735.05	15.37
Cash on hand		137.00	—
<i>Cash in Bank</i> —End of Year		\$1,598.05	\$15.37

* Paid \$10.00 instead of \$25.00 for 1950.

† Salaries were actually \$200.00 less \$41.50 Social Security and withholding taxes not paid at end of year.

AUDITOR'S REPORT

179

CHANGES IN MEMBERSHIP AND RECONCILIATION WITH DUES PAID Year ended December 31, 1951

<i>Changes in Membership</i>	<i>Life</i>	<i>Hon- orary</i>	<i>Educa- tional</i>	<i>Active</i>	<i>Sus- taining</i>	<i>Total</i>
<i>Membership January 1, 1951</i>	1	9	77	398	24	509
<i>Add:</i>						
Elected for 1951 membership at Fall 1950 meeting of board of trustees				3		3
Elected for 1951 membership at June 1951 meeting of board of trustees		1	6	28	2	37
1951 dues paid—prior year unpaid			1	1		2
Reinstated members			6	23	1	30
Unlocated difference			1	1		2
Totals	1	10	91	454	27	583
<i>Deduct:</i>						
Deceased in 1951		1		1		2
Resigned in 1951			1	2		3
Memberships lapsed for nonpayment of dues:*			5	13	1	19
Members at first of year			1	2		3
Members elected for 1951						
Totals	—	1	7	18	1	27
	1	9	84	436	26	556
<i>Changes in classes of memberships:</i>						
From Active to Sustaining				(7)	7	
From Sustaining to Active				9	(9)	
From Educational to Active			(6)	6		
			(6)	8	(2)	
<i>Membership December 31, 1951</i>	1	9	78	444	24	556
<i>Reconciliation with dues paid</i>						
<i>Dues for 1951 Paid in 1950</i>				3		3
<i>Dues Paid in 1951 for 1951:</i>						
Life and Honorary	\$ Waived 1	9				10
Educational at \$2.00 each	160.00		80			80
Active at \$5.00 each	2,215.00			443		443
Sustaining at \$25.00 each	600.00				24	24
\$ 2,975.00	1	9	80	446	24	560
<i>Deduct:</i>						
Duplicate payment of 1951 dues—paid in 1950, re- funded to member in 1951				1		1
Duplicate payment of 1951 dues in 1951, refunded to member in 1951			1	1		2
Check returned by bank			1			1
			2	2		4
	1	9	78	444	24	556

* Under the constitution, dues must be paid to obtain educational, active or sustaining membership.

SUMMARY OF MEMBERSHIP BY YEARS TO DECEMBER 31, 1951

Years Ended December 31:	Total Members	Years Ended December 31:	Total Members
1951	556	1940	270
1950	*509	1939	268
1949	*474	1938	272
1948	422	1937	249
1947	306	1936	240
1946	324	1935	245
1945	† -	1934	230
1944	283	1933	219
1943	† -	1932	203
1942	281	1931	193
1941	279	1930	134

* Excludes dues-paying memberships lapsed for nonpayment of dues.

† Not available, due to wartime dislocation.

HISTORY

The association was incorporated on July 20, 1936, under the laws of the state of New York. However, it had been an unincorporated group for some years earlier, operating under a constitution and related bylaws, which were embodied in the certificate of incorporation. The association has no shareholders and is exempt from federal, state, and local taxes. However, it is required to file a federal information return reporting the source and disposition of income annually.

COMMENTS ON EXAMINATION

Cash receipts as recorded in the cash book were traced into the bank. Dues shown as paid were checked to individual membership cards. Cash from this source was reconciled to the total number of members shown on the official list which is to be furnished individual members. Cash on hand at the end of the year was traced into bank and we verified the balance on deposit on that date directly with the depository.

We inspected the U. S. bonds and verified interest by count of coupons attached. Matured coupons amounting to \$250.00, through December 31, 1951, were found affixed. These were clipped and deposited in bank in the presence of our representative on May 27, 1952. We found no feasible means of verifying independently the amount of proceeds from the banquet.

Disbursements were found to be supported by cancelled checks, receipted bills, and other data.

We also examined the insurance policy, minutes of meetings, and such other data as were pertinent.

GENERAL

Although formal action in documented form did not appear to have been taken with regard to the Proctor Medal Fund, we were advised that it is the intention of the donor that the fund be kept intact as to principal and the income used to defray cost of a medal to be presented periodically for outstanding accomplishment in ophthalmology. The financial provisions of this condition have been met as to the year under examination as well as during the prior year, which also was examined by us.

We have been further advised that the income is to go into the general fund and payment for the medal annually is to come from that fund, with the general fund to make up any difference in cost of the medal above the income of the Proctor Fund.

Present income of the Proctor Fund from bonds is \$250.00 yearly. During 1951, the coupons were not clipped and deposited. Instead, \$175.00 of coupons which matured in 1950 were detached and deposited. Those which matured in 1951, as previously mentioned in this text, were deposited in 1952.

The cost of the Proctor Medal in 1951 was \$150.56. In view of the balance of the income being available this year for other uses, it would be well for the board of trustees to ratify formally the depositing of the bond income in the general fund as a matter of policy.

Constitutional provisions as to bond of the secretary-treasurer and an annual audit by a certified public accountant were found to have been complied with. A federal information return for 1951 was prepared.

Authorization by the board of trustees was found for unusual expenditures during 1951.

All financial activity during the year appeared to be reflected in the accounts and all assets similarly appeared to have been recorded. The only debt or commitment due by the association on December 31, 1951, was Federal Social Security and withholding taxes for the third and fourth quarters, 1951, in the amount of \$41.50 which was paid on March 4, 1952. We obtained a certificate from the secretary-treasurer attesting to the correctness of these statements.

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1952

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 Alvaro, Moacyr Eyck, 1151 Rua Consolacao, São Paulo, Brazil.
 Alvis, Edmund B., 308 N. 6th St., St. Louis 1, Mo.
 Ames, Adelbert, Jr., Dartmouth College, Hanover, N.H.
 Anderson, Banks, Duke Hosp., Durham, N.C.
 Anderson, Edwin R., 514 W. 3rd Ave., Warren, Pa.
 Applebaum, Alfred, 5905 Pacific Blvd., Huntington Park, Calif.
 Armstrong, Richard C., 595 E. Colorado St., Pasadena 1, Calif.
 Ascher, Charles K. W., 2914 Vernon Pl., Cincinnati 19, Ohio.
 Atkinson, George S., 307 First Avenue E., Oskaloosa, Iowa.
 Atkinson, Walter S., 129 Clinton St., Watertown, N.Y.
 Auten, Hanford L., Hitchcock Clinic, Hanover, N.H.

B

Bahn, Charles A., 1210 Maison Blanche Bldg., New Orleans, La.
 Bahn, Gustav C., 1028 Maison Blanche Bldg., New Orleans, La.
 Baird, J. Mason, 511 Medical Arts Bldg., Atlanta, Ga.
 Baldwin, Laurence G., 101 S. Madison, Pasadena 1, Calif.
 Ballantine, Elmer R., 2065 Adelbert Rd., Cleveland 6, Ohio.
 Barber, Aelita N., Dept. Path., LSA Med. Sch., New Orleans, La.
 Batkan, Hans, 2400 Clay St., San Francisco 15, Calif.
 Barkan, Otto, 490 Post St., San Francisco 2, Calif.
 Barnett, Irving F., 30 N. Michigan Ave., Chicago 2, Ill.
 Barrere, Luciano E., Avenida Arenales 22559, Lima, Peru.
 Bassen, Edward J., 70 E. 66th St., New York, N.Y.
 Bedell, Arthur J., 344 State St., Albany, N.Y.
 Beetham, Wm. P., 108 Bay State Rd., Boston, Mass.
 Bell, Dudley P., 411 30th St., Oakland, Calif.
 Bell, Richard P., Jr., 11621 Detroit Ave., Cleveland 2, Ohio.
 Bellows, John G., 30 N. Michigan Blvd., Chicago 2, Ill.
 Benedict, Wm. L., Mayo Clinic, Rochester, Minn.
 Benson, Clifton E., 245 Fourth St., Bremerton, Wash.
 Benton, Curtis D., Jr., Grady Clay Memorial Eye Clinic, Atlanta, Ga.

¹ Attended 1952 Meeting

² Honorary Member

³ Life Member

⁴ Sustaining Member

⁵ Educational Member

Berens, Conrad, 708 Park Ave., New York, N.Y.
 Bergmann, Robert B., 1225 E. Montauk Highway, West Islip, N.Y.
 Berry, A. Erwin, 1846 Teaneck Rd., Teaneck, N.J.
 Bettman, Jerome W., 2400 Clay St., San Francisco 15, Calif.
 Billings, Robert J., Jenkins Arcade Bldg., Pittsburgh 22, Pa.
 Bizzell, James W., Halloran VA Hosp., Staten Island, N.Y.
 Blake, Eugene M., 303 Whitney Ave., New Haven 11, Conn.
 Blankstein, Samuel S., 203 E. Wisconsin Ave., Milwaukee, Wis.
 Blazar, Howard A., U. of Pa. Hosp., Philadelphia, Pa.
 Blodi, Frederick C., University Hosp., Iowa City, Iowa.
 Bloomenthal, Sanford R., Halloran VA Hosp., Staten Island, N.Y.
 Bloomerfield, Sylvan, 1010 Fifth Ave., New York 28, N.Y.
 Blum, John, 44, Blvd. des Tranchees, Geneva, Switzerland.
 Boles, W. M., 1206 Pere Marquette Bldg., New Orleans, La.
 Bonadia, Calogero, Halloran VA Hosp., Staten Island, N.Y.
 Bonner, Wm. R., 3 W. White St., Summit Hill, Pa.
 Borley, W. E., 655 Sutter St., San Francisco 2, Calif.
 Boyd, James L., 10 Edge Hill Rd., Glen Cove, L.I., N.Y.
 Boyes, Truman L., 654 Madison Ave., New York, N.Y.
 Braley, Alton E., University Hosp., Iowa City, Iowa.
 Brandenburg, K. C., 110 Pine Ave., Long Beach 2, Calif.
 Brandman, Samuel R., 804 Rose Building, Cleveland, Ohio.
 Brault, Jules, 418 E. Sherbrooke St., Montreal, Canada.
 Brav, Solomon S., 2027 Spruce St., Philadelphia, Pa.
 Brecher, Gerhard A., Dept. Physiology, Western Reserve Univ. Med. Sch., Cleveland, Ohio.
 Breinin, Goodwin M., 3 E. 66th St., New York 21, N.Y.
 Brennan, James W., 88 W. Utica St., Buffalo, N.Y.
 Bribach, E. J., 603 Commercial St., Atchison, Kan.
 Bronk, Henry N., 708 Park Ave., New York 21, N.Y.
 Brown, Albert L., 1137 Carew Tower, Cincinnati 2, Ohio.
 Brown, E. V. L., 122 S. Michigan Ave., Chicago, Ill.
 Browning, Charles V., Univ. of Oregon Med. Sch., Portland, Ore.
 Bruner, Abram B., 1214 Guardian Bldg., Cleveland, Ohio.
 Bryan, James H., 3720 Washington Blvd., St. Louis 8, Mo.
 Budd, Francis N., 4040 W. 58th St., Cleveland, Ohio.
 Buesseler, John A., Fairchild Airforce Base, Spokane, Wash.
 Bulson, Eugene L., 347 W. Berry St., Fort Wayne, Ind.
 Burch, Edward P., 424 Hamm Bldg., St. Paul, Minn.
 Burdick, J. J., 105 Seville Blvd., Lafayette, La.
 Burian, Hermann M., University Hosp., Iowa City, Iowa.
 Burke, John W., 2000 Massachusetts Ave. N.W., Washington 6, D.C.
 Burnett, Arthur R., 310 Burr Bldg., New Castle, Ind.
 Burr, Sherwood P., Jr., 43 E. Jackson St., Tucson, Ariz.
 Butler, J. B. V., 909 Medical Dental Bldg., Portland, Ore.
 Buxeda, Roberto, 303 De Diego Ave., Santurce, Puerto Rico.
 Byrnes, Victor A., Sch. of Aviation Med., Randolph Field, Tex.

C

Calhoun, F. Plumby, 478 Peachtree St., Atlanta 3, Ga.
 Calkins, Larry L., 3215 W. 69th St., Kansas City 5, Mo.

Calahan, Alston,⁶ Univ. of Ala. Med. Col., Birmingham, Ala.
 Campion, George S., 490 Post St., San Francisco 2, Calif.
 Carrasquillo, Honorio F., Medical Arts Bldg., Puerta de Tierra, Puerto Rico.
 Carroll, Frank D., Blind Brook Lodge, Rye, N.Y.
 Carter, George Z., 545 W. 111th St., Apt. 9F, New York 25, N.Y.
 Cary, Edward H., 631 Medical Arts Bldg., Dallas, Tex.
 Casten, Virgil G., 412 Beacon St., Boston 15, Mass.
 Castroviejo, Ramon, 9 E. 91st St., New York 28, N.Y.
 Caylor, Robert N.,⁶ Medical Arts Bldg., El Paso, Tex.
 Chace, Robert R., 635 W. 165th St., New York 32, N.Y.
 Chalfant, W. Paxson, Jr., 1228 16th St. N.W., Washington 6, D.C.
 Chamberlain, Webb P., Jr.,⁴ 1324 Hanna Bldg., Cleveland 2, Ohio.
 Chambers, Arthur L., II,⁶ EEN&T Clinic, U. S. Army Hosp., Ft. Hood, Tex.
 Chandler, Paul A., 5 Bay State Rd., Boston 15, Mass.
 Chan-Pong, Norman R., Maraval, Trinidad, B.W.I.
 Chapman, Vernon A., Palm Springs, Calif.
 Chickering, Donald H., 1842 Forest Hill Blvd., East Cleveland, Ohio.
 Chisholm, Julian F., Jr., 34½ Beacon St., Boston, Mass.
 Cholst, Mortimer,⁶ 1 Nevins St., Brooklyn, N.Y.
 Christensen, Leonard,⁶ Univ. of Ore. Med. Sch., Portland, Ore.
 Christiansen, Gordon S., University Hosp., Iowa City, Iowa.
 Clapp, Clyde A.,³ 513 N. Charles St., Baltimore 1, Md.
 Clark, Charles E.,⁶ 207 S. Commerce, Natchez, Miss.
 Clark, Wm. B.,³ 211 S. Saratoga Ave., New Orleans, La.
 Clothier, Wm. L., 407 Kane Bldg., Pocatello, Idaho.
 Cloutier, Roland, Medical Arts Bldg., Montreal 25, Quebec.
 Cogan, David G.,³ 243 Charles St., Boston, Mass.
 Colson, Z. Wm., 301 Essex St., Lawrence, Mass.
 Constantine, F. H., 30 W. 59th St., New York 19, N.Y.
 Constantine, K. W., 229 Barton Ave., Palm Beach, Fla.
 Cordes, Frederick C., 384 Post St., San Francisco 8, Calif.
 Courtney, R. H., 501 Franklin St., Richmond, Va.
 Courvoisier, Earl A., 55 E. Washington St., Chicago, Ill.
 Covey, John K., 140 W. High St., Bellefonte, Pa.
 Cowan, Alfred, 1930 Chestnut St., Philadelphia, Pa.
 Craig, Paul C., 232 N. 5th St., Reading, Pa.
 Crawford, H. C., 705 Doctors Bldg., Atlanta 3, Ga.
 Crawford, Joseph W., 490 Post St., San Francisco, Calif.
 Crawford, Walter J., 3910 Market St., Riverside, Calif.
 Cregar, John S., 440 Harrison St., East Orange, N.J.
 Cross, George H., 525 Welsh St., Chester Pa.
 Culler, Arthur M., 150 E. Broad St., Columbus, Ohio.
 Cumming, Mrs. Edith L., Valley Cottage, N.Y.
 Curtain, Brain J. H.,⁶ 447 E. 14th St., New York 9, N.Y.
 Cushman, Beulah,¹ 25 E. Washington St., Chicago 2, Ill.
 Cutler, Morton, 1515 Addison Ave., E., Twin Falls, Idaho.

D

D'Amico, Thomas V.,⁶ 70 Fairview Ave., Verona, N.J.
 Dasilva, Antonio L., Rua Santa Catarina 1101, Belo Horizonte, Minas Gerais, Brazil, S.A.
 Davies, Robert H., 634 Washington Rd., Pittsburgh 28, Pa.
 Day, R. M.,⁶ 635 W. 165th St., New York 32, N.Y.
 Dayton, Glenn O., Jr.,⁶ 1052 W. 6th, Los Angeles, Calif.
 de Andrade, Cesario,⁶ Bahia, Brazil.
 DeFrancois, Walter,⁶ 122 So. Michigan Ave., Chicago 3, Ill.
 DeLong, Samuel L.,⁶ University Hosp., Philadelphia 4, Pa.
 Dennis, Richard H., 33 College Ave., Waterville, Me.
 DeOcampo, Geminiano, P.I. Hosp., Manila, P.I.
 deSoto Nary, Ilona K.,¹ 158 Whitney Ave., New Haven 11, Conn.
 DeVoe Arthur G., 30 W. 59th St., New York 32, N.Y.
 DeWitt, Edward N., 881 LaFayette St., Bridgeport 4, Conn.
 Dickson, Owen C., 2628 Telegraph Ave., Berkeley, Calif.
 Dillahun, Jack A., 106 S. Girard, Albuquerque, N.M.
 Dische, Zacharias,⁶ 630 W. 168th St., New York, N.Y.
 Diskan, Samuel M., 1616 Pacific Ave., Atlantic City, N.J.
 Dixon, Joseph M., 2156 Highland Ave., Birmingham, Ala.
 Doherty, William R., 150 W. 55th St., New York, N.Y.
 Dolphin, Joseph M.,⁶ Brooklyn Eye Hosp., Brooklyn 5, N.Y.
 Downing Arthur H., 406 Sixth Ave., Des Moines, Iowa.
 Dreik, Maurice J., 630 Med. Arts Bldg., Seattle 1, Wash.

Duane, Thomas D., Bedminster, Pa.
 Dugan, J. Winston,⁶ University Hosp., Edmonton, Alberta, Canada.
 Duke-Elder, Lady Phyllis,² London, England.
 Duke-Elder, Sir Stewart,² London, England.
 Dunnavan, Floyd L., 514 Medical Arts Bldg., Vancouver, Wash.
 Dunnington, John H., 635 W. 165th St., New York 32, N.Y.
 Dunphy, Edwin B., 243 Charles St., Boston, Mass.
 Durham, Davis G., Medical Arts Bldg., Wilmington, Del.
 Dwiggin, Horace G., Veterans Hosp., Tuskegee, Ala.
 Dyar, Edwin W., 3202 N. Meridian St., Indianapolis 8, Ind.
 Dyson, Charles, 283 Queens Ave., London, Ontario, Canada.

E

Ehrenfeld, Edward, 185 Lexington Ave., Passaic, N.J.
 Elles, Norma B., 800 Travis St., Houston 2, Tex.
 Elliot, Alfred J., 170 St. George St., Toronto, Canada.
 Ellis, Orwyn H., 523 W. 6th St., Los Angeles 14, Calif.
 Elvin, Norman L., 309 Med. Arts Bldg., Winnipeg, Manitoba, Canada.
 Emerson, George O., Jr.,⁶ 218 Second Ave., New York 3, N.Y.
 Engel, Samuel, 350 Post St., San Francisco 8, Calif.
 Ernst, Marie K.,⁶ 1411 S. Albany Ave., Tampa 6, Fla.
 Esposito, Albert C. M., 1212 First Huntington Natl. Bank Bldg., Huntington, W.Va.
 Esterman, Benjamin, 983 Park Ave., New York, N.Y.
 Evans, John N.,² 23 Schermerhorn St., Brooklyn 2, N.Y.
 Evans, Wm. H., 510 Dollar Bank Bldg., Youngstown, Ohio.

F

Falls, Harold F., University Hosp., Ann Arbor, Mich.
 Feamster, Robert C., 13½ E. Choctaw Ave., McAlester, Okla.
 Ferrer, Horatio,² Havana, Cuba.
 Fine, Max, 655 Sutter St., San Francisco 2, Calif.
 Fink, Austin I., 110 Remsen St., Brooklyn 2, N.Y.
 Fink, Walter H.,¹ 1921 Med. Arts Bldg., Minneapolis 2, Minn.
 Finkelstein, Julius,⁶ 1521 Delachaise, New Orleans, La.
 Fisher, James A. Jr.,⁶ 601 Grand Avenue, Asbury Park, N.J.
 Fitzgerald, James R., 30 N. Michigan Ave., Chicago, Ill.
 Fixott, R. S., Lt. Col. USAF (MC), USAF Hosp., Scott Air Force Base, Ill.
 Flanagan, Roger M., Univ. of Oregon Med. Sch., Portland, Ore.
 Elick, John J., 1443 N. Pennsylvania, Indianapolis, Ind.
 Flynn, John E.,⁶ 526 E. 20th St., New York 9, N.Y.
 Flynn, Gregory E.,⁶ New Haven Hosp., New Haven, Conn.
 Fonda, G. E.,⁶ 6 Parkview Dr., Millburn, N.J.
 Foote, Franklin M.,¹ 1790 Broadway, New York, N.Y.
 Forrest, Robert L.,⁶ Walter Reed Army Med. Center, Ocular Research Unit, Washington, D.C.
 Fralick, F. Bruce, 408 1st Natl. Bank Bldg., Ann Arbor, Mich.
 Franks, Myron B.,⁶ 401 Hotel Jamestown Bldg., Jamestown, N.Y.
 Freeman, Sheldon B.,⁶ 196 Linwood Ave., Buffalo, N.Y.
 Friedell, H. L., 2065 Adelbert Rd., Cleveland, Ohio.
 Friedenwald, Jones S.,⁶ 1212 Eutaw Pl., Baltimore 17, Md.
 Friedman, Benjamin, 160 W. 73rd St., New York 24, N.Y.
 Frink, Berton F., Suite 2, M. & J. Nelson Bldg., McAllen, Tex.
 Fruttschi, Ulrich A., 523 Medico-Dental Bldg., Sacramento 14, Calif.

G

Gallardo, Edward, 153 Marquette St., LaSalle, Ill.
 Gans, Jerome A., 723 Osborn Bldg., Cleveland 15, Ohio.
 Gans, Morris E., 1621 Euclid Ave., Cleveland 15, Ohio.
 Garron, Levon K.,⁶ 426 17th St., Oakland 12, Calif.
 Gehrsitz, Leta B.,⁶ 3435 S.W. 12th Ave., Portland 1, Ore.
 Gifford, Harold, 1620 Med. Arts Bldg., Omaha, Neb.
 Gilbert, Ralph H., 110 Fulton St., E., Grand Rapids 2, Mich.
 Gilger, Anita P.,⁶ 6396 W. Bucyrus Dr., Cleveland 9, Ohio.
 Gill, Earl K., 806 Medical-Professional Bldg., Corpus Christi, Tex.

Irvine, A. Ray, Los Angeles, Calif.
 Johnson, Lorand V., Cleveland, Ohio.
 Kahler, Arthur R., Sacramento, Calif.
 McCallum, George C., Eugene, Ore.
 McConnell, Malcolm A., Minneapolis, Minn.
 McDonald, P. Robb, Philadelphia, Pa.
 Marshall, M. R., Edmonton, Alberta, Canada
 Minsky, Henry, New York, N.Y.
 Payne, Brittain F., New York, N.Y.
 Reese, Algernon B., New York, N.Y.

Reid, John J., Jr., New York, N.Y.
 de Roethth, Andrew F. M., Spokane, Wash.
 Smith, E. Terry, West Hartford, Conn.
 Thomas, Harry V., Clarksburg, W. Va.
 Thorpe, Harvey E., Pittsburgh, Pa.
 Thygeson, Phillips, San Jose, Calif.
 Trueman, Robert H., Philadelphia, Pa.
 Vail, Derrick, Chicago, Ill.
 Yudkin, Arthur M., New Haven, Conn.
 Zekman, Theodore N., Chicago, Ill.

MEMBERS

A

Abraham, Samuel V., 6363 Wilshire Blvd., Los Angeles 36, Calif.
 Abrams, Henry, 195 Nassau St., Princeton, N.J.
 Addington, Charles H., 675 Delaware Ave., Buffalo, N.Y.
 Adler, Francis H.,^{1,4} 313 S. 17th St., Philadelphia, Pa.
 Aiken, Samuel D., 384 Post St., San Francisco 8, Calif.
 Albaugh, Clarence H., 727 W. 7th St., Los Angeles 14, Calif.
 Allerstadt, Norbert F., 921 Commerce Bldg., Erie, Pa.
 Alexander, Robert L., Euclid Ave. at 93rd St., Cleveland 6, Ohio.
 Allen, James H.,^{1,4} 1430 Tulane Ave., New Orleans, La.
 Allen, Lee,⁸ University Hosp., Iowa City, Iowa.
 Allen, Robert T., Indiana Univ. Medical Center, Indianapolis, Ind.
 Allen, Thomas D.,¹ 2329 Pioneer Rd., Evanston, Ill.
 Alvaro, Moacyr Eyck, 1151 Rua Consolacao, São Paulo, Brazil.
 Alvis, Edmund B., 308 N. 6th St., St. Louis 1, Mo.
 Ames, Adelbert, Jr., Dartmouth College, Hanover, N.H.
 Anderson, Banks, Duke Hosp., Durham, N.C.
 Anderson, Edwin R.,¹ 514 W. 3rd Ave., Warren, Pa.
 Applebaum, Alfred, 5905 Pacific Blvd., Huntington Park, Calif.
 Armstrong, Richard C., 595 E. Colorado St., Pasadena 1, Calif.
 Ascher, Charles K. W.,¹ 2914 Vernon Pl., Cincinnati 19, Ohio.
 Atkinson, George S.,¹ 307 First Avenue E., Oskaloosa, Iowa.
 Atkinson, Walter S., 129 Clinton St., Watertown, N.Y.
 Auten, Hanford L., Hitchcock Clinic, Hanover, N.H.

B

Bahn, Charles A., 1210 Maison Blanche Bldg., New Orleans, La.
 Bahn, Gustav C., 1028 Maison Blanche Bldg., New Orleans, La.
 Baird, J. Mason, 511 Medical Arts Bldg., Atlanta, Ga.
 Balding, Laurence G., 101 S. Madison, Pasadena 1, Calif.
 Ballintine, Elmer J., 2065 Adelbert Rd., Cleveland 6, Ohio.
 Barber, Aetela N., Dept. Path., LSA Med. Sch., New Orleans, La.
 Batkan, Hans, 2400 Clay St., San Francisco 15, Calif.
 Barkan, Otto, 490 Post St., San Francisco 2, Calif.
 Barnett, Irving F., 30 N. Michigan Ave., Chicago 2, Ill.
 Barrere, Luciano E.,¹ Avenida Arenales #2559, Lima, Peru.
 Bassen, Edward J., 70 E. 66th St., New York, N.Y.
 Bedell, Arthur J.,¹ 344 State St., Albany, N.Y.
 Beetham, Wm. P., 108 Bay State Rd., Boston, Mass.
 Bell, Dudley P., 411 30th St., Oakland, Calif.
 Bell, Richard P., Jr., 11621 Detroit Ave., Cleveland 2, Ohio.
 Bellows, John G.,¹ 30 N. Michigan Blvd., Chicago 2, Ill.
 Benedict, Wm. L.,¹ Mayo Clinic, Rochester, Minn.
 Benson, Clifton E., 245 Fourth St., Bremerton, Wash.
 Benton, Curtis D., Jr.,¹ Grady Clay Memorial Eye Clinic, Atlanta, Ga.

¹ Attended 1952 Meeting² Honorary Member³ Life Member⁴ Sustaining Member⁸ Educational Member

Berens, Conrad,^{1,2} 708 Park Ave., New York, N.Y.
 Bergmann, Robert B., 1225 E. Montauk Highway, West Islip, N.Y.
 Berry, A. Erwin,¹ 1846 Teaneck Rd., Teaneck, N.J.
 Bettman, Jerome W., 2400 Clay St., San Francisco 15, Calif.
 Billings, Robert J., Jenkins Arcade Bldg., Pittsburgh 22, Pa.
 Bizzell, James W., Halloran VA Hosp., Staten Island, N.Y.
 Blake, Eugene M.,¹ 303 Whitney Ave., New Haven 11, Conn.
 Blankstein, Samuel S.,¹ 203 E. Wisconsin Ave., Milwaukee, Wis.
 Blazar, Howard A., U. of Pa. Hosp., Philadelphia, Pa.
 Blodi, Frederick C., University Hosp., Iowa City, Iowa.
 Bloenthal, Sanford R., Halloran VA Hosp., Staten Island, N.Y.
 Bloomerfield, Sylvan, 1010 Fifth Ave., New York 28, N.Y.
 Blum, John, 44, Blvd. des Tranchees, Geneva, Switzerland.
 Boles, W. M., 1206 Pere Marquette Bldg., New Orleans, La.
 Bonadia, Calogero, Halloran VA Hosp., Staten Island, N.Y.
 Bonner, Wm. R., 3 W. White St., Summit Hill, Pa.
 Borley, W. E., 655 Sutter St., San Francisco 2, Calif.
 Boyd, James L., 10 Edge Hill Rd., Glen Cove, L.I., N.Y.
 Boyes, Truman L.,^{1,4} 654 Madison Ave., New York, N.Y.
 Braley, Alton E.,¹ University Hosp., Iowa City, Iowa.
 Brandenburg, K. C., 110 Pine Ave., Long Beach 2, Calif.
 Brandwan, Samuel R., 804 Rose Building, Cleveland, Ohio.
 Brault, Jules, 418 E. Sherbrooke St., Montreal, Canada.
 Bray, Solomon S., 2027 Spruce St., Philadelphia, Pa.
 Brecher, Gerhard A.,¹ Dept. Physiology, Western Reserve Univ. Med. Sch., Cleveland, Ohio.
 Breinin, Goodwin M., 3 E. 66th St., New York 21, N.Y.
 Brennan, James W., 88 W. Utica St., Buffalo, N.Y.
 Bribach, E. J., 603 Commercial St., Atchison, Kan.
 Bronk, Henry N., 708 Park Ave., New York 21, N.Y.
 Brown, Albert L., 1137 Carew Tower, Cincinnati 2, Ohio.
 Brown, E. V. L., 122 S. Michigan Ave., Chicago, Ill.
 Browning, Charles V.,¹ Univ. of Oregon Med. Sch., Portland, Ore.
 Bruner, Abram B., 1214 Guardian Bldg., Cleveland, Ohio.
 Bryan, James H., 3720 Washington Blvd., St. Louis 8, Mo.
 Budd, Francis X., 4040 W. 58th St., Cleveland, Ohio.
 Buesseler, John A., Fairchild Airforce Base, Spokane, Wash.
 Bulson, Eugene L., 347 W. Berry St., Fort Wayne, Ind.
 Burch, Edward P., 424 Hamm Bldg., St. Paul, Minn.
 Burdin, J. J.,¹ 105 Seville Blvd., Lafayette, La.
 Durian, Hermann M.,¹ University Hosp., Iowa City, Iowa.
 Burke, John W., 2000 Massachusetts Ave. N.W., Washington 6, D.C.
 Burnett, Arthur B.,¹ 310 Burr Bldg., New Castle, Ind.
 Burr, Sherwood P., Jr., 43 E. Jackson St., Tucson, Ariz.
 Butler, J. B. V., 909 Medical Dental Bldg., Portland, Ore.
 Buxeda, Roberto, 303 De Diego Ave., Santurce, Puerto Rico.
 Byrnes, Victor A., Sch. of Aviation Med., Randolph Field, Tex.

C

Calhoun, F. Pliminy, 478 Peachtree St., Atlanta 3, Ga.
 Calkins, Larry L., 3215 W. 69th St., Kansas City 5, Mo.

Calahan, Alston,⁴ Univ. of Ala. Med. Col., Birmingham, Ala.
 Campion, George S., 490 Post St., San Francisco 2, Calif.
 Carrasquillo, Honorio F., Medical Arts Bldg., Puerta de Tierra, Puerto Rico.
 Carroll, Frank D., Blind Brook Lodge, Rye, N.Y.
 Carter, George Z., 545 W. 111th St., Apt. 9F, New York 25, N.Y.
 Cary, Edward H., 631 Medical Arts Bldg., Dallas, Tex.
 Casten, Virgil G., 412 Beacon St., Boston 15, Mass.
 Castroviejo, Ramon, 9 E. 91st St., New York 28, N.Y.
 Caylor, Robert N.,⁶ Medical Arts Bldg., El Paso, Tex.
 Chace, Robert R., 635 W. 165th St., New York 32, N.Y.
 Chalfant, W. Paxson, Jr., 1228 16th St. N.W., Washington 6, D.C.
 Chamberlain, Webb P., Jr.,⁴ 1324 Hanna Bldg., Cleveland 2, Ohio.
 Chambers, Arthur L., II,⁶ EEN&T Clinic, U. S. Army Hosp., Ft. Hood, Tex.
 Chandler, Paul A., 5 Bay State Rd., Boston 15, Mass.
 Chan-Pong, Norman K., Maraval, Trinidad, B.W.I.
 Chapman, Vernon A., Palm Springs, Calif.
 Chickering, Donald H., 1842 Forest Hill Blvd., East Cleveland, Ohio.
 Chisholm, Julian F., Jr., 34½ Beacon St., Boston, Mass.
 Cholat, Mortimer,⁶ 1 Nevins St., Brooklyn, N.Y.
 Christensen, Leonard,⁶ Univ. of Ore. Med. Sch., Portland, Ore.
 Christiansen, Gordon S., University Hosp., Iowa City, Iowa.
 Clapp, Clyde A.,⁵ 513 N. Charles St., Baltimore 1, Md.
 Clark, Charles E.,⁶ 207 S. Commerce, Natchez, Miss.
 Clark, Wm. B.,³ 211 S. Saratoga Ave., New Orleans, La.
 Clothier, Wm. L., 407 Kane Bldg., Pocatello, Idaho.
 Cloutier, Roland, Medical Arts Bldg., Montreal 25, Quebec.
 Cogan, David G.,³ 243 Charles St., Boston, Mass.
 Colson, Z. Wm., 301 Essex St., Lawrence, Mass.
 Constantine, F. H., 30 W. 59th St., New York 19, N.Y.
 Constantine, K. W., 229 Barton Ave., Palm Beach, Fla.
 Cordes, Frederick C., 384 Post St., San Francisco 8, Calif.
 Courtney, R. H., 501 Franklin St., Richmond, Va.
 Courvoisier, Earl A., 55 E. Washington St., Chicago, Ill.
 Covey, John K., 140 W. High St., Bellefonte, Pa.
 Cowan, Alfred, 1930 Chestnut St., Philadelphia, Pa.
 Craig, Paul C., 232 N. 5th St., Reading, Pa.
 Crawford, H. C., 705 Doctors Bldg., Atlanta 3, Ga.
 Crawford, Joseph W., 490 Post St., San Francisco, Calif.
 Crawford, Walter J., 3910 Market St., Riverside, Calif.
 Cregar, John S., 440 Harrison St., East Orange, N.J.
 Cross, George H., 525 Welsh St., Chester Pa.
 Culler, Arthur M., 150 E. Broad St., Columbus, Ohio.
 Cumming, Mrs. Edith L., Valley Cottage, N.Y.
 Curtain, Brain J. H.,⁴ 447 E. 14th St., New York 9, N.Y.
 Cushman, Beulah,³ 25 E. Washington St., Chicago 2, Ill.
 Cutler, Morton, 1515 Addison Ave., E., Twin Falls, Idaho.

D

D'Amico, Thomas V.,⁶ 70 Fairview Ave., Verona, N.J.
 Dasilva, Antonio L., Rua Santa Catarina 1101, Belo Horizonte, Minas Gerais, Brazil, S.A.
 Davies, Robert H., 634 Washington Rd., Pittsburgh 28, Pa.
 Day, R. M.,⁶ 635 W. 165th St., New York 32, N.Y.
 Dayton, Glenn O., Jr.,⁶ 1052 W. 6th, Los Angeles, Calif.
 de Andrade, Cesario,⁶ Bahia, Brazil.
 DeFrancois, Walter,⁶ 122 So. Michigan Ave., Chicago 3, Ill.
 DeLong, Samuel L.,⁶ University Hosp., Philadelphia 4, Pa.
 Dennis, Richard H., 33 College Ave., Waterville, Me.
 DeOcampo, Geminiano, Phil. Gen. Hosp., Manila, P.I.
 deSuto Nagy, Ilona K.,³ 158 Whitney Ave., New Haven 11, Conn.
 DeVoe, Arthur G., 30 W. 59th St., New York 32, N.Y.
 DeWitt, Edward N., 881 LaFayette St., Bridgeport 4, Conn.
 Dickson, Owen C., 2628 Telegraph Ave., Berkeley, Calif.
 Dillahun, Jack A., 106 S. Girard, Albuquerque, N.M.
 Dische, Zacharias,⁶ 630 W. 168th St., New York, N.Y.
 Diskan, Samuel M., 1616 Pacific Ave., Atlantic City, N.J.
 Dixon, Joseph M., 2156 Highland Ave., Birmingham, Ala.
 Doherty, William R., 150 W. 55th St., New York, N.Y.
 Dolphin, Joseph M.,⁶ Brooklyn Eye Hosp., Brooklyn 5, N.Y.
 Downing, Arthur H., 406 Sixth Ave., Des Moines, Iowa.
 Dreli, Maurice J., 630 Med. Arts Bldg., Seattle 1, Wash.

Duane, Thomas D., Bedminster, Pa.
 Duggan, J. Winston,⁶ University Hosp., Edmonton, Alberta, Canada.
 Duke-Elder, Lady Phyllis,³ London, England.
 Duke-Elder, Sir Stewart,³ London, England.
 Dunnavan, Floyd L., 514 Medical Arts Bldg., Vancouver, Wash.
 Dunnington, John H., 635 W. 165th St., New York 32, N.Y.
 Dunphy, Edwin R., 243 Charles St., Boston, Mass.
 Durham, Davis G., Medical Arts Bldg., Wilmington, Del.
 Dwiggin, Horace G., Veterans Hosp., Tuskegee, Ala.
 Dyar, Edwin W., 3202 N. Meridian St., Indianapolis 8, Ind.
 Dyson, Charles, 283 Queens Ave., London, Ontario, Canada.

E

Ehrenfeld, Edward, 185 Lexington Ave., Passaic, N.J.
 Elles, Norma B., 800 Travis St., Houston 2, Tex.
 Elliot, Alfred J., 170 St. George St., Toronto, Canada.
 Ellis, Orwyn H., 523 W. 6th St., Los Angeles 14, Calif.
 Elvin, Norman L., 309 Med. Arts Bldg., Winnipeg, Manitoba, Canada.
 Emerson, George O., Jr.,⁶ 218 Second Ave., New York 3, N.Y.
 Engel, Samuel, 350 Post St., San Francisco 8, Calif.
 Ernst, Marie K.,⁶ 1411 S. Albany Ave., Tampa 6, Fla.
 Esposito, Albert C. M., 1212 First Huntington Natl. Bank Bldg., Huntington, W.Va.
 Esterman, Benjamin, 983 Park Ave., New York, N.Y.
 Evans, John N.,³ 23 Schermerhorn St., Brooklyn 2, N.Y.
 Evans, Wm. H., 510 Dollar Bank Bldg., Youngstown, Ohio.

F

Falls, Harold F., University Hosp., Ann Arbor, Mich.
 Feamster, Robert C., 13½ E. Choctaw Ave., McAlester, Okla.
 Ferrer, Horatio,⁶ Havana, Cuba.
 Fine, Max, 655 Sutter St., San Francisco 2, Calif.
 Fink, Austin I., 110 Remsen St., Brooklyn 2, N.Y.
 Fink, Walter H.,³ 1921 Med. Arts Bldg., Minneapolis 2, Minn.
 Finkelstein, Julius,⁶ 1521 Delachaise, New Orleans, La.
 Fisher, James A. Jr.,⁶ 601 Grand Avenue, Asbury Park, N.J.
 Fitzgerald, James R., 30 N. Michigan Ave., Chicago, Ill.
 Fixott, R. S., Lt. Col. USAF (MC), USAF Hosp., Scott Air Force Base, Ill.
 Flanagan, Roger M., Univ. of Oregon Med. Sch., Portland, Ore.
 Flick, John J., 1443 N. Pennsylvania, Indianapolis, Ind.
 Flynn, John E.,⁶ 526 E. 20th St., New York 9, N.Y.
 Flynn, Gregory E.,⁶ New Haven Hosp., New Haven, Conn.
 Fonda, G. E.,⁶ 6 Parkview Dr., Millburn, N.J.
 Foote, Franklin M.,³ 1790 Broadway, New York, N.Y.
 Forrest, Robert L.,⁶ Walter Reed Army Med. Center, Ocular Research Unit, Washington, D.C.
 Fralick, F. Bruce, 408 1st Natl. Bank Bldg., Ann Arbor, Mich.
 Franks, Myron B.,⁶ 401 Hotel Jamestown Bldg., Jamestown, N.Y.
 Freeman, Sheldon B.,³ 196 Linwood Ave., Buffalo, N.Y.
 Friedell, H. L., 2065 Adelbert Rd., Cleveland, Ohio.
 Friedenwald, Jones S.,³ 1212 Eutaw Pl., Baltimore 17, Md.
 Friedman, Benjamin, 160 W. 73rd St., New York 24, N.Y.
 Frink, Berton F., Suite 2, M. & J. Nelson Bldg., McAllen, Tex.
 Fritsch, Ulrich A., 523 Medico-Dental Bldg., Sacramento 14, Calif.

G

Gallardo, Edward, 153 Marquette St., LaSalle, Ill.
 Gans, Jerome A., 723 Osborn Bldg., Cleveland 15, Ohio.
 Gans, Morris E., 1621 Euclid Ave., Cleveland 15, Ohio.
 Garron, Levon K.,⁶ 426 17th St., Oakland 12, Calif.
 Gehrsitz, Leta B.,⁶ 3435 S.W. 12th Ave., Portland 1, Ore.
 Gifford, Harold, 1620 Med. Arts Bldg., Omaha, Neb.
 Gilbert, Ralph H., 110 Fulton St., E., Grand Rapids 2, Mich.
 Gilger, Anita P.,³ 6396 W. Bucyrus Dr., Cleveland 9, Ohio.
 Gill, Earl K., 806 Medical-Professional Bldg., Corpus Christi, Tex.

Gillette, David F., 109 S. Warren St., Syracuse, N.Y.
 Ginsberg, Joseph,⁸ Mass. Eye & Ear Infirmary, Boston 14, Mass.
 Givner, Isadore, 108 E. 66th St., New York 16, N.Y.
 Goar, Everett L., 1304 Walker Ave., Houston 2, Tex.
 Goff, John L., Los Alamos Med. Center, Los Alamos, N.M.
 Goldberg, Sol, 8082 Jenkins Arcade, Pittsburgh, Pa.
 Goodfellow, Thomas J., 20 Arcade Bldg., Saratoga Springs, N.Y.
 Gordon, Dan M., 525 E. 68th St., New York 21, N.Y.
 Gowens, Harry L. Jr., 2217 Delancey St., Philadelphia, Pa.
 Graham, John H., 4275 Pearl Rd., Cleveland 9, Ohio.
 Grant, Hendrie, W., 330 Lowry Medical Arts Bldg., St. Paul, Minn.
 Grant, W. Morton, 243 Charles St., Boston 14, Mass.
 Gray, John E.,⁸ 2615 Capitol Ave., Sacramento 16, Calif.
 Griffey, Edward W.,⁸ 217 Hermann Professional Bldg., Houston, Tex.
 Guerry, dePont III, 7102 Glen Pkwy., Richmond, Va.
 Guibor, George P.,⁸ 30 N. Michigan Ave., Chicago 2, Ill.
 Gundersen, Trygve,⁸ 101 Bay State Rd., Boston 15, Mass.
 Guy, Loren P.,⁸ 40 E. 62nd St., New York 21, N.Y.
 Guyton, Jack S., Johns Hopkins Hosp., Baltimore 5, Md.

H

Haas, Joseph S.,⁸ 109 N. Wabash Ave., Chicago, Ill.
 Haessler, F. Herbert, 545 N. 15th St., Milwaukee 3, Wis.
 Haik, George M.,⁸ 812 Maison Blanche Bldg., New Orleans, La.
 Hall, Thomas G.,⁸ 516 Sutter St., San Francisco 2, Calif.
 Hallett, Joseph W., Medical Arts Bldg., Philadelphia, Pa.
 Haney, Lawrence O.,⁸ 100 E. St. Vrain St., Colorado Springs, Colo.
 Hanson, A. George, 1528 Medical Dental Bldg., Seattle 1, Wash.
 Hardesty, Hiram H., 10515 Carnegie Ave., Cleveland 6, Ohio.
 Hardesty, John F., 634 N. Grand Blvd., St. Louis, Mo.
 Hardy, LeGrand H., 23 E. 79th St., New York, N.Y.
 Hare, James,⁸ Crile V. A. Hosp., Cleveland, Ohio.
 Hare, Robert, 416 N. Bedford Dr., Beverly Hills, Calif.
 Harger, Robert W.,⁸ 1100 Med. Grp., Hdq. Command, Bolling Air Force Base, Washington 25, D.C.
 Harley, Halvor L., 101 S. Indiana Ave., Atlantic City, N.J.
 Harley, Robison D., 101 S. Indiana Ave., Atlantic City, N.J.
 Harrington, David O., 384 Post St., San Francisco 8, Calif.
 Harris, John E.,⁸ Dept. of Ophthalmology, Uni. of Oregon Med. Sch., Portland, Ore.
 Hart, Clinton E.,⁸ 145 Elk Pl., New Orleans, La.
 Hartenbower, G. E.,⁸ 410 Unity Bldg., Bloomington, Ill.
 Hartman, Deane C., 727 W. 7th St., Los Angeles 14, Calif.
 Hartshorne, Isaac, 30 W. 59th St., New York 19, N.Y.
 Harvey, Elmer F., 942 Hanna Bldg., Cleveland 15, Ohio.
 Hawks, Gordon H.,⁸ 100 College St., Toronto, Ontario, Canada.
 Heare, Louis C., 207 Medical Bldg., Port Arthur, Tex.
 Heath, Parker,⁸ 243 Charles St., Boston 14, Mass.
 Hebbard, Frederick W., 153 Wallace Ave., Vallejo, Calif.
 Heitger, Joseph D., 701 Heyburn Bldg., Louisville, Ky.
 Henderson, John W.,⁸ 102 Second Ave., S.W., Rochester, Minn.
 Henderson, John W., University Hosp., Ann Arbor, Mich.
 Henderson, Lawrence E., 502 Electric Bldg., Watertown, N.Y.
 Henry, Alvin L.,⁸ 621 Franklin St., Columbus, Ind.
 Henry, Margaret, 384 Post St., San Francisco 8, Calif.
 Hester, Marion W., 1255 Lakeland Hills Blvd., Lakeland, Fla.
 Hildreth, H. Rommel, 3720 Washington Blvd., St. Louis 8, Mo.
 Hilgartner, H. L., 202 W. 13th St., Austin, Tex.
 Hill, Howard F., Professional Bldg., Waterville, Me.
 Hill, John M.,⁸ 218 Second Ave., New York, N.Y.
 Hill, Robert V., 1329 Broadway, Longview, Wash.
 Hirsch, Monroe J., 950 W. Jefferson Blvd., Los Angeles 7, Calif.
 Hofstetter, Henry W., Div. of Optometry, Ind. Univ., Bloomington, Ind.
 Hogan, Michael J., 450 Sutter St., San Francisco, Calif.

Holmer, Dorothy B., 1816 R. St., N.W., Washington 9, D.C.
 Holmes, W. P., 45 Alexander Young Blvd., Honolulu 9, T.H.
 Holstein, Theodore, 411 Medico-Dental Bldg., Sacramento 14, Calif.
 Holzer, Wm. F., 36 Pleasant St., Worcester 8, Mass.
 Horwich, Harry,⁸ 200 E. 26th St., New York 10, N.Y.
 Hosford, George N., 450 Sutter St., San Francisco, Calif.
 Howard, Harvey J., 1000 S. Fort Harrison Ave., Clearwater, Fla.
 Howell, Homer P., 3022 E. 14th St., Oakland 1, Calif.
 Hughes, Wm. F. Jr.,⁸ 536 Sheridan Rd., Evanston, Ill.
 Hurwitz, Paul, 55 E. Washington St., Chicago 2, Ill.

I

Imus, Henry A., Office of Naval Research, U. S. Navy 100, F.P.O., New York, N.Y.
 Ingalls, Raymond G., 59 Church St., Berlin, N.H.
 Insel, Herman H., 770 Fidelity Med. Bldg., Dayton 2, Ohio.
 Irvine, A. Ray,⁸ 727 W. 7th St., Los Angeles 14, Calif.
 Irvine, Rodman, 727 W. 7th St., Los Angeles 14, Calif.
 Irvine, Wendell C.,⁸ 727 W. 7th St., Los Angeles 14, Calif.

J

Jacobs, Clyde H., Gen. F. Geisinger Mem. Hosp., Danville, Pa.
 Jacobson, Jerry H., Capt. USAF (MC),⁸ 3320 Med. Group, Amarillo, Air Force Base, Tex.
 Jacoby, M. W., 1364 Hanna Bldg., Cleveland 15, Ohio.
 Jakobovits, Rafael, 655 Sutter St., San Francisco 2, Calif.
 James, Wm. M., 3720 Washington Blvd., St. Louis 8, Mo.
 Jampolsky, Arthur J., 2400 Clay St., San Francisco 15, Calif.
 Jensen, Carl D. F., 1315 Medical-Dental Bldg., Seattle 1, Wash.
 Johns, Juanita P., 313 Commonwealth Ave., Boston, Mass.
 Johnson, Hobart C., 839 Belgrade Ave., Mankato, Minn.
 Johnson, Lorand V.,⁸ 10515 Carnegie, Cleveland 6, Ohio.
 Johnson, Samuel B.,⁸ 145 Elk Pl., New Orleans 12, La.
 Judd, John H., 1020 Medical Arts Bldg., Omaha, Neb.

K

Kadin, Maurice, 535 Main St., Racine, Wis.
 Kahan, Edmund,⁸ 200 W. 93rd St., New York, N.Y.
 Kahler, Arthur R.,⁸ 2615 Capitol Ave., Sacramento 16, Calif.
 Katz, Dewey, 99 Pratt St., Hartford 3, Conn.
 Katzin, Herbert M.,⁸ 11 E. 68th St., New York 21, N.Y.
 Key, Samuel N. Jr., 120 W. 7th St., Austin, Tex.
 Keyes, John E. L., 22199 McCauley Rd., Shaker Hgts., Cleveland 22, Ohio.
 Kilgore, George L., 3314 Fourth St., San Diego, Calif.
 King, George L., 537 E. Market St., Alliance, Ohio.
 King, John H. Jr., Chief of Ophthalmology, Walter Reed Army Hosp., Washington 12, D.C.
 Kinsey, V. Everett,⁸ Kresge Eye Institute, 690 Mullett St., Detroit 26, Mich.
 Kirby, Daniel B.,⁸ 780 Park Ave., New York 21, N.Y.
 Kirk, Robert C.,⁸ 3399 Warren Rd., Cleveland, Ohio.
 Kirkland, T. N. Jr.,⁸ 6234 Curie, New Orleans, La.
 Knapp, Arthur A., 907 5th Ave., New York 21, N.Y.
 Knighton, Willis S., 121 E. 61st St., New York, N.Y.
 Knowles, F. Edwin Jr., 513 N. Charles St., Baltimore 1, Md.
 Koch, F. L. P., 60 E. 75th St., New York 21, N.Y.
 Koenig, Ivan J., 40 North St., Buffalo 2, N.Y.
 Kornzweig, Abraham L., 1200 5th Ave., New York, N.Y.
 Kottler, Saul, 831 Guardian Bldg., Cleveland 14, Ohio.
 Krause, Arlington C., 950 E. 59th St., Chicago, Ill.
 Krewson, William E. III, 1930 Chestnut St., Philadelphia 3, Pa.
 Kronenberg, Bernard, 737 Park Ave., New York, N.Y.
 Kronfeld, Peter C., 109 N. Wabash Ave., Chicago 2, Ill.
 Krug, Joseph H., 988 Fifth Ave., New York 21, N.Y.
 Kuhn, Hedwig S., 60 Glendale Park, Hammond, Ind.

L

Lachman, George S., 450 Sutter St., San Francisco, Calif.
 Laird, Robert G., Metz Bldg., Grand Rapids 2, Mich.
 Lake, Max S., United Bldg., Salina, Kan.
 Lang, Louis R., 555 Park Ave., New York, N.Y.
 Lang, Richard E., 463 Passaic Ave., Passaic, N.J.

Larkin, Bernard J., 305 Hume Mansur Bldg., Indianapolis 4, Ind.
 Last, Murray A., 1095 Park Ave., New York, N.Y.
 Laval, Joseph, 136 E. 64th St. New York, N.Y.
 Leckert, E. L. Jr., 211 S. Saratoga Ave., New Orleans 12, La.
 Lee, Otis, Springer Clinic, Tulsa, Okla.
 Legett, Carey Jr., 1707 Colorado, Austin, Tex.
 Leinfelder, P. J., University Hosp., Iowa City, Iowa.
 Lemoine, Albert N., 411 Alameda Rd., Country Club Plaza, Kansas City 2, Mo.
 Lemoine, Albert N. Jr., 411 Alameda Rd., Kansas City, Mo.
 Leopold, Irving H., 1930 Chestnut St., Philadelphia 3, Pa.
 Lepard, C. W., 1025 David Whitney Bldg., Detroit 26, Mich.
 Lerner, Macy L., 332 Park Ave., Rochester 7, N.Y.
 Levy, Abram, 1401 Plainfield Ave., South Plainfield, N.J.
 LeWin, Thurber, 112 Linwood Ave., Buffalo, N.Y.
 Lewis, Philip M., Exchange Bldg., Memphis 3, Tenn.
 Lieberman, Sumner David, 114 Bay State Rd., Boston 15, Mass.
 Linn, Jay G. Jr., 7075 Jenkins Arcade Bldg., Pittsburgh 22, Pa.
 Linn, Jay G. Sr., 7075 Jenkins Arcade, Pittsburgh 22, Pa.
 Lipp, Frank E., 830 City Natl. Bank Bldg., Omaha 2, Neb.
 Little, Milton F., 85 Jefferson St., Hartford, Conn.
 Lloyd, Ralph I., 14 Eighth St., Brooklyn 17, N.Y.
 Locke, John C., 1414 Drummond St., Montreal, Quebec, Canada.
 Lordan, John P., 9730 Wilshire Blvd., Beverly Hills, Calif.
 Loutfall, Michel, 1826 State St., Santa Barbara, Calif.
 Luedde, Philip S., Hampton Village Med. Center, St. Louis 2, Mo.
 Lühr, John P., 625 Linwood Ave., Buffalo, N.Y.
 Lutzman, Frank C., Germantown Professional Bldg., Philadelphia 44, Pa.
 Lyda, Wood, 812 Maison Blanche Bldg., New Orleans, La.
 Lyle, Donald J., 601 Union Trust Bldg., Cincinnati 2, Ohio.

Mc

McAlester, A. W. III, 2003 Bryant Bldg., Kansas City, Mo.
 McAlpine, Paul T., 129 Summit Ave., Summit, N.J.
 McBain, Earle H., 490 Post St., San Francisco 2, Calif.
 McCallum, George C., 431 Eugene Medical Center, Eugene, Ore.
 McCamel, Malcolm A., 1918 Medical Arts Bldg., Minneapolis 2, Minn.
 McClure, G. David, U. S. Army Hosp., Camp McCoy, Wis.
 McCulloch, Clement, 830 Med. Arts Bldg., Toronto, Ontario, Canada.
 McDonald, P. Robb, 1930 Chestnut St., Philadelphia 3, Pa.
 McGarvey, W. E., 802 Jackson City Bank Bldg., Jackson, Mich.
 McGavic, John S., 601 Montgomery Ave., Bryn Mawr, Pa.
 McGowan, William L., 510 Union Central Bldg., Cincinnati 2, Ohio.
 McGuire, H. H., 105 N. Braddock St., Winchester, Va.
 McGuire, Wm. P., 105 N. Braddock St., Winchester, Va.
 McKay, Edward D., Scott and White Clinic, Temple, Tex.
 McKee, Joseph W., 1105 Grand Ave., Kansas City 6, Mo.
 McLean, John M., 525 E. 68th St., New York 21, N.Y.
 McMurray, John B., 6 S. Main St., Washington, Pa.
 McRae, John H., Medical Arts Bldg., Grand Rapids 2, Mich.

M

MacDonald, Alexander, 421 Med. Arts Bldg., Toronto, Ontario, Canada.
 MacDonald, Roy K., 15 Walsley Blvd., Toronto, Ontario, Canada.
 MacLean, Angus L., 1201 N. Calvert St., Baltimore 2, Md.
 Macnie, John P., 635 W. 165th St., New York 32, N.Y.
 Madeley, H. Randall, 727 Sonoma St., Vallejo, Calif.
 Magee, George R., 1331 Hillside Dr., Reno, Nev.
 Makley, Torrence A., University Hosp., Columbus, Ohio.
 Mallek, Howard, 924 Vancouver Block, Vancouver, B.C.
 Mandelbaum, Joseph, 101 Lafayette Ave., Brooklyn 17, N.Y.

Mann, Wm. A., 30 N. Michigan Ave., Chicago 2, Ill.
 Mannis, Aaron A., 109 N. Wabash Ave., Chicago, Ill.
 Marcus, Arthur A., 30 E. 40th St., New York, N.Y.
 Marg, Elwin, 226 Vine Rd., R.R. 1, Medway, Ohio.
 Marshall, M. R., Wells pavilion, University Hosp., Edmonton, Alberta, Canada.
 Martz, George E., 608 N. 3rd St., Harrisburg, Pa.
 Masters, Robert J., 805 Hume Mansur Bldg., Indianapolis 4, Ind.
 Matthews, John L., 929 Nix Professional Bldg., San Antonio 5, Tex.
 Maumance, Alfred E., Stanford University Hosp., San Francisco 15, Calif.
 Meisenbach, Albert E. Jr., 300 Medical Arts Bldg., Dallas 9, Tex.
 Merriam, George R. Jr., 635 W. 165th St., New York 32, N.Y.
 Mesirov, M. E., 117 E. Cook St., Santa Maria, Calif.
 Meyer, George P., 410 Haddon Ave., Camden, N.J.
 Meyer, Samuel J., 109 N. Wabash Ave., Chicago 2, Ill.
 Miles, Paul W., 640 S. Kingshighway, St. Louis 10, Mo.
 Miller, Claude K., 30 S. Wenatchee St., Wenatchee, Wash.
 Miller, George L., 14805 Detroit Ave., Lakewood, Ohio.
 Miller, Miriam, 350 Post St., San Francisco 8, Calif.
 Mills, Dawson A., U. S. Naval Hosp., Newport, R.I.
 Mills, Lloyd, 609 S. Grand Ave., Los Angeles, Calif.
 Mims, James L. Jr., Medical Arts Bldg., San Antonio, Tex.
 Minnes, James F., 825 Granville St., Vancouver, B.C.
 Minsky, Henry, 960 Park Ave., New York, N.Y.
 Monahan, Robert H., 1034 Lowry Med. Arts Bldg., St. Paul, Minn.
 Moncreiff, Wm. F., 58 E. Washington St., Chicago, Ill.
 Moore, Paul G., 1701 Republic Bldg., Cleveland, Ohio.
 Morgan, James C. Jr., 145 Elk Pl., New Orleans, La.
 Morgan, Meredith, W. Jr., 911 MacDonald Ave., Richmond, Calif.
 Morris, Jean, W., Johnston Bldg., Muncie, Ind.
 Morrison, W. Howard, 1500 Med. Arts Bldg., Omaha 2, Neb.
 Mortensen, A. V. N., 458 Government St., Mobile 12, Ala.
 Motto, M. Paul, 650 Rose Bldg., Cleveland 15, Ohio.
 Mullen, Carroll R., 2025 Locust St., Philadelphia 3, Pa.
 Myers, Roscoe, W., 36 Pleasant St., Worcester 8, Mass.

N

Nadlath, Rudolph P., U. S. Naval Hosp., Portsmouth, Va.
 Nelson, Robert C., 14058 Superior Rd., Cleveland Heights 18, Ohio.
 Nethercut, Glenway W., 25 E. Washington St., Chicago 2, Ill.
 Newell, Frank W., 30 N. Michigan Ave., Chicago 2, Ill.
 Nicholl, Russell J., 10515 Carnegie Ave., Cleveland 6, Ohio.
 Noble, Bertha R., 1206 Pere Marquette Bldg., New Orleans, La.
 Noe, Carl A., 601 Higley Bldg., Cedar Rapids, Iowa.
 Norene, Robert A., 727 W. 7th St., Los Angeles 14, Calif.
 Norton, Herman J. Jr., 409 University Park, Rochester, N.Y.
 Nosik, Wm. A., 10515 Carnegie Ave., Cleveland 6, Ohio.
 Novak, Joseph F., 807 Empire Bldg., Pittsburgh 22, Pa.
 Nugent, Maurice W., 2007 Wilshire Blvd., Los Angeles 5, Calif.

O

Oakley, Kenneth H., 129 N. Jackson St., Roseburg, Ore.
 Oaks, Lewis W., 677 N. University Ave., Provo, Utah.
 O'Brien, Cecil S., 43 E. Jackson St., Tucson, Ariz.
 O'Brien, James M., 735 Clinton Ave., Bridgeport, Conn.
 Odom, Robert E., 247 Charlotte St., Asheville, N.C.
 Ogile, Kenneth N., Mayo Clinic, Rochester, Minn.
 Ohly, John H., 22 Schermerhorn St., Brooklyn 2, N.Y.
 Ormsby, Hugh L., 75 Sutherland Dr., Leaside, Toronto, Ont., Canada.
 O'Rourke, Donald H., 920 Republic Bldg., Denver 2, Colo.
 Osler, Jay K., 5 Grove St., Bangor, Me.
 Owens, Wm. C., Johns Hopkins Hosp., Baltimore 5, Md.
 Ozment, Thomas L., Box 3, Letterman Army Hosp., San Francisco, Calif.

P

Pang, Herbert G., 52 S. Vineyard St., Honolulu, T.H.
 Parker, Walter R., 1551 Woodward Ave., Detroit, Mich.

- Paton, R. Townley, 927 Park Ave., New York 28, N.Y.
 Patterson, John W.,¹ 2105 Adelbert Rd., Cleveland, Ohio.
 Paul, Thomas O., 2205 Highland Ave., Birmingham 5, Ala.
 Payne, Brittain F.,¹ 17 E. 72nd St., New York 21, N.Y.
 Perera, Charles A., 70 E. 66th St., New York, N.Y.
 Pettit, Wm. A., 727 W. 7th St., Los Angeles, Calif.
 Pfingst, Harry A., 1015 Heyburn Bldg., Louisville 2, Ky.
 Phillips, Josephine D., 2010 E. 102nd St., Cleveland 6, Ohio.
 Pichette, Henri,² 425 St. John St., Quebec City, Quebec, Canada.
 Pinkoson, Charles,² 926 S. W. Second Ave., Gainesville, Fla.
 Pischel, Dohrmann K.,¹ 490 Post St., San Francisco 2, Calif.
 Plumer, John S., 121 University Pl., Pittsburgh 13, Pa.
 Polan, Charles M., 1042 Sixth Ave., Huntington, W.Va.
 Posner, Adolph, 667 Madison Ave., New York 21, N.Y.
 Post, Lawrence T., 508 No. Grand Blvd., St. Louis 3, Mo.
 Post, Martin H. Jr.,¹ 520 Metropolitan Bldg., St. Louis, Mo.
 Potter, Wm. B., 521 22nd St., Galveston, Tex.
 Potts, Albert M., Dept. of Surgery, Western Reserve Univ., Cleveland 6, Ohio.
 Prangen, Avery D.,¹ Mayo Clinic, Rochester, Minn.
 Pushkin, Edward A., 122 S. Michigan Ave., Chicago, Ill.
- R
- Radewan, Milton G., 30 S. Wenatchee Ave., Wenatchee, Wash.
 Raffo, Julio C., Gremios #465, Lima, Peru, S.A.
 Ralph, Fenn T.,¹ 193 Clinton Ave., Brooklyn, N.Y.
 Rasgorshke, Robert H., 425 Aquila Ct., Omaha, Neb.
 Ravdin, Emile M., 4036 Wilshire Blvd., Los Angeles 5, Calif.
 Redding, Willis A., Towanda, Pa.
 Reeder, James E. Jr., 523 Davidson Bldg., Sioux City 13, Iowa.
 Reeb, Merrill J., 919 S.W. Taylor St. Bldg., Portland 5, Ore.
 Reese, Algernon B.,² 73 E. 71st St., New York 21, N.Y.
 Reese, Warren S., 2118 Locust St., Philadelphia 3, Pa.
 Regan, James J., 520 Commonwealth Ave., Boston 15, Mass.
 Reid, Frederick K., 500 N. George St., Rome, N.Y.
 Reid, Horace W., 2205 Union Central Bldg., Cincinnati 2, Ohio.
 Reid, John J. Jr.,¹ 105 E. 63rd St., New York 21, N.Y.
 Reitz, Herbert R., 446 Linwood Ave., Buffalo, N.Y.
 Riddle, Ransford J., 14 Porter Way, Sharon, Pa.
 Riffenburgh, Ralph S., U. S. Naval Hosp., Mare Island, Vallejo, Calif.
 Rigg, James P., 521 Rood Ave., Grand Junction, Colo.
 Robbins, Alfred R., 1930 Wilshire Blvd., Los Angeles 5, Calif.
 Roberts, Walter L., 8225 Ramsgate, Los Angeles, Calif.
 Rodin, Frank H., 490 Post St., San Francisco 2, Calif.
 de Roeth, Andrew F. M.,¹ 1006 Overbluff, Spokane, Wash.
 de Roeth, Andrew, Jr.,² 635 W. 165th St., New York 32, N.Y.
 Romaine, Hunter, 111 E. 65th St., New York 21, N.Y.
 Romejko, Walter J., 1810 K St., N.W., Washington 6, D.C.
 Rones, Benjamin, 1601 Eye St., N.W., Washington, D.C.
 Roper, Kenneth L.,¹ 55 E. Washington St., Chicago 2, Ill.
 Rosen, Emanuel P., 692 High St., Newark, N.J.
 Rosenbaum, Harry D., 3720 Washington Blvd., St. Louis, Mo.
 Rosenberg, Abner S., 142 Jerusalem St., Brooklyn 2, N.Y.
 Rosenthal, Benj. C., 140 New York Ave., Brooklyn 16, N.Y.
 Rosner, Robert S., 10300 Carnegie Ave., Cleveland 6, Ohio.
 Ross, Cecelia, 1318 Second St., Santa Monica, Calif.
 Ross, Joseph V. M., 321 E. Front St., Berwick, Pa.
 Rothen, Robert M.,¹ 145 Elk Pl., New Orleans, La.
 Rouse, David M.,¹ 500 W.C.U. Building, Quincy, Ill.
 Row, Hamilton D., 906 Hume Mansur Bldg., Indianapolis 4, Ind.
 Rowland, Louise S., Johns Hopkins Hosp., Baltimore 5, Md.
 Rucker, C. Wilbur, Mayo Clinic, Rochester, Minn.
 Ruedemann, A. D., 1633 David Whitney Bldg., Detroit 26, Mich.
 Rutherford, Cyrus W.,¹ 4601 N. Pennsylvania St., Indianapolis, Ind.
 Ryan, Wm. F., 520 Commonwealth Ave., Boston 15, Mass.
 Rychener, Ralph O., 130 Madison Ave., Memphis 3, Tenn.
- S
- Sacks-Wilner, Erwin, 225 W. State St., Trenton, N.J.
 Sakler, Barnet R., 19 Garfield Pl., Cincinnati 2, Ohio.
 Saltzman, Samuel L., 334 W. 86th St., New York 24, N.Y.
 Samuels, Bernard, 57 W. 57th St., New York, N.Y.
 Sanders, T. E.,¹ 3720 Washington Blvd., St. Louis 8, Mo.
 Sauer, John J., 30 E. 40th St., New York, N.Y.
 Scala, Norman P., 901 20th St., N.W., Washington 6, D.C.
 Scarney, Herman D., 573 Fisher Bldg., Detroit 2, Mich.
 Schachat, Walter S., 39 E. 75th St., New York 22, N.Y.
 Scheie, Harold G.,¹ 313 S. 17th St., Philadelphia 3, Pa.
 Schepens, Charles L., 243 Charles St., Boston, Mass.
 Schlaegel, Theodore F., Jr., Ind. Univ. Med. Center, Indianapolis, Ind.
 Schlossman, Abraham, 667 Madison Ave., New York 21, N.Y.
 Schmerl, Ernst, 2805 Otis Ave., Toledo 6, Ohio.
 School, Robert E.,¹ 211 S. Saratoga Ave., New Orleans 12, La.
 Scholz, Roy O., 11 E. Chase St., Baltimore 2, Md.
 Schonberg, Albert L., 414 N. Adams, Albuquerque, N.M.
 Schrimp, Cyril E., 2500 Clifton Ave., Cincinnati, Ohio.
 Schultz, Jacob F., 1304 Walker Ave., Houston, Tex.
 Schuster, Stephen A., 1st Natl. Bank Bldg., El Paso, Tex.
 Schwartz, Frank E.,¹ Walter Reed General Hosp., Washington, D.C.
 Schwartz, Frederick O., 508 N. Grand Blvd., St. Louis 3, Mo.
 Schwarz, Gerald T.,¹ 10515 Carnegie Ave., Cleveland 6, Ohio.
 Sezer, F. Necolet,¹ Cerrohpasa Hosp., Istanbul, Turkey.
 Shaffer, Robert N., 490 Post St., San Francisco 2, Calif.
 Shahan, Philip T., 508 N. Grand Ave., St. Louis 3, Mo.
 Shahan, Wm. E., 508 N. Grand Blvd., St. Louis 3, Mo.
 Shannon, C. E. G., 1930 Chestnut St., Philadelphia, Pa.
 Shapira, Theodore M.,¹ 109 N. Wabash Ave., Chicago 2, Ill.
 Shapiro, Ernest K.,¹ 20-57 18th St., Long Island City 5, N.Y.
 Sharbaugh, George B., 212 W. State St., Trenton 8, N.J.
 Sheard, Charles, P.O. Box 543, Rochester, Minn.
 Sheppard, L. Benjamin, 301 Medical Arts Bldg., 2nd and Franklin Sts., Richmond 19, Va.
 Sherman, A. Russell, 671 Broad St., Newark, N.J.
 Sherman, Elbert S., 671 Broad St., Newark, N.J.
 Shoch, David E.,¹ N.W. Univ. Medical School, Chicago, Ill.
 Shusterman, Morris, 100 College St., Toronto, Ontario, Canada.
 Siegel, Edward, 81 Brinkerhoff St., Plattsburg, N.Y.
 Simonton, John T., 108-41 63rd Dr., Forest Hills, L.I., N.Y.
 Sitchevska, Olga, 30 Fifth Ave., New York 11, N.Y.
 Sitney, Julian J., 6363 Wilshire Blvd., Los Angeles 48, Calif.
 Skow, John D., 2001 Collingwood Ave., Toledo 2, Ohio.
 Slabaugh, Carlyle R., Indianapolis Gen. Hosp., Indianapolis, Ind.
 Sloar, Henry L., 106 W. 7th St., Charlotte 2, N.C.
 Smith, Byron, 927 Park Ave., New York, N.Y.
 Smith, E. Gerard, 324 N. Duke St., Lancaster, Pa.
 Smith, Hiram J., 30 N. Michigan Ave., Chicago, Ill.
 Smith, Homer E., 508 E. S. Temple St., Salt Lake City 1, Utah.
 Smith, James W., 1016 Fifth Ave., New York 28, N.Y.
 Smith, Jaroud B., Jr., Comdr., M.D., U.S.N., 1006 Church St., Alva, Okla.
 Smith, John T., BuMed., Navy Dept., Washington 25, D.C.
 Smith, Joseph G., 450 Sutter St., San Francisco 8, Calif.
 Smithson, Robert A., Jr., 1530 Arizona Ave., Santa Monica, Calif.
 Snell, Albert C., 53 S. Fitzhugh St., Rochester, N.Y.
 Snyder, Daniel, 109 N. Wabash Ave., Chicago 2, Ill.
 Snyder, M. Wilson, 14 Porter Way, Sharon, Pa.
 Sommers, Ignatius G., 981 S. Westmoreland Ave., Los Angeles 6, Calif.
 Spaeth, Edmund B., 1930 Chestnut St., Philadelphia, Pa.
 Spiegelglass, A. B., 417 Main St., Hackensack, N.J.
 Stauffer, Harry B., 234 Madison St., Jefferson City, Mo.
 Steinberg, Abraham, 323 Jenkins Bldg., Pittsburgh 22, Pa.
 Steinberg, Bernhard, 2805 Otis Ave., Toledo 6, Ohio.
 Steinberg, Theodore, 603 Patterson Bldg., Fresno, Calif.
 Stevens, Ralph W., Baker Bldg., Walla Walla, Wash.

Stillerman, Manuel L.,² 109 N. Wabash Ave., Chicago 2, Ill.
 Stine, George T., 327 E. State St., Columbus 16, Ohio.
 Stoddard, Kenneth B., School of Optometry, Univ. of Calif., Berkeley, Calif.
 Stokes, Wm. H., 1620 Medical Arts Bldg., Omaha, Neb.
 Stolz, Irwin H., Natl. City Bank Bldg., Cleveland, Ohio.
 Stone, Wm., Jr., 1101 Beacon St., Brookline, Mass.
 Streicher, Carl J., 217 Park Pl., Ashtabula, Ohio.
 Streit, August J., 724 Polk St., Amarillo, Tex.
 Sugar, H. Saul, 311 Kales Bldg., Detroit 26, Mich.
 Suie, Ted,² Dept. of Bacteriology, Ohio State Univ., Columbus, Ohio.
 Sullivan, Charles T., 277 Alexander St., Rochester 7, N.Y.
 Sullivan, John V., 207 United Bldg., Akron 8, Ohio.
 Swab, Charles M., 1316 Medical Arts Bldg., Omaha, Neb.
 Swan, Kenneth C., 3181 S.W. Marquam Hill Rd., Portland 1, Ore.
 Sykowski, Peter S., 1330 Union St., Schenectady 8, N.Y.

T

Tait, Edwin F.,³ 1324 W. Main St., Norristown, Pa.
 Tallot, Thomas E.,² Univ. of Oregon Medical Sch., Portland, Ore.
 Tanner, Owen R., Homer Ave., Palo Alto, Calif.
 Tassman, Isaac S., 711 Medical Arts Bldg., Philadelphia, Pa.
 Taylor, E. Merle, 1220 S.W. Taylor, Portland, Ore.
 Theobald, Georgiana D., 715 Lake St., Oak Park, Ill.
 Theodore, Frederick H., 667 Madison Ave., New York 21, N.Y.
 Thigpen, Charles A., 401 S. Court St., Montgomery 5, Ala.
 Thomas, Charles I., 10505 Carnegie Ave., Cleveland 6, Ohio.
 Thomas, Edward R., 60 Wyoming St., Dayton, Ohio.
 Thomas, Harry V., Empire Bank Bldg., Clarksburg, W.Va.
 Thomas, John H., 262 E. Market St., Warren, Ohio.
 Thomas, Maxwell, 206 Medical Arts Bldg., Dallas, Tex.
 Thompson, Edward H., 19 W. 7th St., Cincinnati, Ohio.
 Thornburgh, Robert G., 517 Prof. Bldg., Long Beach, Calif.
 Thorpe, Harvey E.,² 323 Jenkins Arcade, Pittsburgh, Pa.
 Thygeson, Phillips,² 87 N. 6th St., San Jose, Calif.
 Tinkess, Donald E., Ituri Towers, Greenwich, Conn.
 Tracht, Robert R., 404 Lowry Medical Arts Bldg., St. Paul 2, Minn.
 Troncoso, Manuel U., 217 S. Ocean Ave., Freeport, L.I., N.Y.
 Trowbridge, Dwight H., Jr., 2900 Fresno St. Building, Fresno, Calif.
 Trueman, Robert H.,² 1917 Panama St., Philadelphia 3, Pa.
 Truhlsen, Stanley M., 1500 Medical Arts Bldg., Omaha, Neb.
 Tusak, Ervin A., 115 E. 90th St., New York 28, N.Y.
 Tyner, George S., Metropolitan Bldg., Denver, Colo.

V

Vail, Derrick,³ 700 N. Michigan Ave., Chicago 11, Ill.
 Van Huenen, J. Alexander, 244 Edwards St., New Haven, Conn.
 Van Wien, Stefan, 104 S. Michigan Blvd., Chicago 3, Ill.
 Vanzant, Thomas J.,³ 1403 Hermann Prof. Bldg., Houston, Tex.
 Veirs, Everett R., Scott & White Clinic, Temple, Tex.
 Velarde, Herminio, Sr., Phil. General Hosp., Manila, P.I.
 Venable, Howard P., 11 N. Jefferson, St. Louis, Mo.

Verhoeff, F. H.,² 395 Commonwealth Ave., Boston, Mass.
 Vesey, Frank Archibald, 1545 Union St., Schenectady, N.Y.
 Vickery, Robert D., 1209 W. Sherwin St., Chicago, Ill.
 Viger, R. J., 1414 Drummond St., Montreal, Canada.
 Vogel, Adolph W., Suburban Square Bldg., Ardmore, Pa.
 Vogel, Herbert P.,² 145 Elks Pl., New Orleans 12, La.
 von Sallmann, Ludwig,³ 635 W. 165th St., New York 32, N.Y.

W

Wald, George, Harvard Biological Lab., Cambridge, Mass.
 Waldman, Joseph, 1930 Chestnut St., Philadelphia 3, Pa.
 Walker, Glenn L., Univ. Hosp., Iowa City, Iowa.
 Walker, O. J., Home Savings & Loan Bldg., Youngstown, Ohio.
 Walling, Harry C., 25 Main St., Binghamton, N.Y.
 Walls, Gordon L., Sch. of Optometry, Univ. of Calif., Berkeley, Calif.
 Watkins, John G., Jr.,² 839 Donaghey Bldg., Little Rock, Ark.
 Waugh, Richey L.,² 1542 Tulane Ave., New Orleans, La.
 Webster, David H., 140 E. 54th St., New York 22, N.Y.
 Weih, Elmer P., 605 Wilson Bldg., Clinton, Iowa.
 Weinberg, Herman C., 2101 S. Taylor Rd., University Hgts., Ohio.
 Weintrob, Joseph R., 1616 Pacific Ave., Atlantic City, N.J.
 Weiss, Herman, 6333 Wilshire Blvd., Los Angeles, Calif.
 Weissner, Charles W., 806 May Bldg., Pittsburgh 22, Pa.
 Wescott, Virgil, 30 N. Michigan Ave., Chicago 2, Ill.
 Wesson, Thomas W., 124 S.E. First St., Evansville 8, Ind.
 Weston, Charles L., 1200 W. Murray St., Macomb, Ill.
 Wetzel, John O., 1012 N. Riverside Dr., St. Clair, Mich.
 Wheeler, Maynard C., 30 W. 59th St., New York, N.Y.
 Whitney, Percy T., 1047 Slater Bldg., Worcester 8, Mass.
 Wilder, Helenor C.,³ Armed Forces Institute of Pathology, Washington 25, D.C.
 Wiley, George A., 202 Security Natl. Bank Bldg., Norman, Okla.
 Wilner, Arthur S., 225 State St., Trenton, N.J.
 Wilson, Fred M.,³ Ind. Univ. Med. Center, Indianapolis, Ind.
 Wilson, Warren A., 1930 Chestnut Blvd., Los Angeles 5, Calif.
 Winger, Ira B., 709 Madison Ave., Toledo 2, Ohio.
 Wolfe, Otis D.,³ 415 Masonic Temple, Marshalltown, Iowa.
 Wolfe, Otis R., 28 S. 1st Ave., Marshalltown, Iowa.
 Wolfe, Russell M., 307 Masonic Temple, Marshalltown, Iowa.
 Wolpaw, Benjamin J., 2323 Prospect Ave., Cleveland 15, Ohio.
 Woods, Alan C., Johns Hopkins Hosp., Baltimore 5, Md.
 Wortham, Edwin, IV, 204 Medical Arts Bldg., Richmond, Va.
 Wyman, George J., 331 Fulton St., Peoria, Ill.

XYZ

Young, Charles A., 409 Medical Arts Bldg., Roanoke, Va.
 Young, Charles A., Jr., 409 Medical Arts Bldg., Roanoke, Va.
 Yudkin, Arthur M.,² 457 Church St., New Haven 10, Conn.
 Zekman, Theodore N.,² 58 E. Washington St., Chicago, Ill.
 Zentmayer, William,² 1930 Chestnut St., Philadelphia 3, Pa.
 Zerfoss, Kate S., Medical Arts Bldg., Nashville, Tenn.

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Row, Hamilton D.
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Schlaegel, Theodore F., Jr.
Slabaugh, Carlyle B.
Wilson, Fred M.
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Morris, Jean W.
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Dowling, Arthur H.
- IOWA CITY
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Blodi, Frederick C.
Braley, Alton E.
Burian, Hermann M.
Christiansen, Gordon S.
Leinfelder, P. J.
Walker, Glenn L.
- MARSHALLTOWN
Wolfe, Otis D.
Wolfe, Otis R.
Wolfe, Russell M.
- OSKALOOSA
Atkinson, George S.
- ST. LOUIS CITY
Reeder, James E., Jr.
- KANSAS
ATCHISON
Bribach, E. J.
- SALINA
Lake, Max S.
- KENTUCKY
LOUISVILLE
Heitger, Joseph D.
Phingst, Harry A.
- LOUISIANA
LAFAYETTE
Burdin, James J.
- NEW ORLEANS
Allen, James H.
Bahn, Gustav C.
Bahn, Charles A.
Barber, Aeleta N.
Boles, W. M.
Clark, William B.
Finkelstein, Julius
Haik, George M.
Hart, Clinton E.
Johnson, Samuel B.
Kirkland, T. N., Jr.
Leckert, E. L., Jr.
Lyda, Wood
Morgan, James C., Jr.
Noble, Bertha Riveroll
Rothen, Robert M.
Schoel, Robert E.
Vogel, Herbert P.
Waugh, Richey L., Jr.
- MAINE
BANGOR
Osler, Jay K.
- WATERVILLE
Dennis, Richard H.
Hill, Howard F.
- MARYLAND
BALTIMORE
Clapp, Clyde A.
Friedenwald, Jonas S.
Guyton, Jack S.
Knowles, F. Elwin, Jr.
MacLean, Angus L.
Owens, Wm. C.
Rowland, Louise S.
Scholz, Roy O.
Woods, Alan C.
- MASSACHUSETTS
BOSTON
Beetham, Wm. P.
Casten, Virgil C.
Chandler, Paul A.
Chisholm, Julian F., Jr.
Cogan, David G.
Dunphy, Edwin B.
Ginsberg, Joseph
Grant, W. Morton
Gundersen, Trygve
Heath, Parker
Johns, Juanita P.
Liebman, Sumner D.
Regan, James J.
Ryan, Wm. F.
Schepens, Charles L.
Verhoeff, F. H.
- BROOKLINE
Stone, William
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Wald, George
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Colson, Z. Wm.
- WORCESTER
Holzer, Wm. F.
Myers, Roscoe W.
Whitney, Percy T.
- MICHIGAN
ANN ARBOR
Falls, Harold F.
Frailick, F. Bruce
Henderson, John W.
- DETROIT
Kinsey, V. Everett
Lepard, C. W.
Parker, Walter R.
Ruedemann, A. D.
Scarney, Herman D.
Sugar, H. Saul
- GRAND RAPIDS
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Gilbert, Ralph H.
Laird, Robert G.
McRae, John H.
- JACKSON
McGarvey, Wm. E.
- ST. CLAIR
Wetzel, John O.
- WILLIAMSBURG
Weih, Jack E.
- MINNESOTA
MANKATO
Johnson, H. C.
- MINNEAPOLIS
Fink, Walter H.
McCannel, Malcolm A.
- ROCHESTER
Benedict, Wm. L.
Henderson, J. W.
Ogle, Kenneth N.
Prangen, Avery D.
Rucker, C. Wilbur
Sheard, Charles
- ST. PAUL
Burch, Edward P.
Grant, Hendrie W.
Monahan, Robert H.
Tracht, Robert R.
- MISSISSIPPI
NATCHEZ
Clark, Charles E.
- MISSOURI
JEFFERSON CITY
Stauffer, Harry B.
- KANSAS CITY
Calkins, Larry L.
Lemoine, Albert N.
Lemoine, Albert N., Jr.
McAlester, A. W., III
McKee, Joseph W.
- ST. LOUIS
Alvis, E. B.
Bryan, James H.
Hardesty, John F.
Hildreth, H. Rommel
James, Wm. M.
Luedde, Philip S.
Miles, P. W.
Post, Lawrence T.
Post, Martin H., Jr.
Rosenbaum, Harry D.
Sanders, T. E.
Schwartz, Frederick O.

- Shahan, Philip T.
Shahan, Wm. E.
Venable, Howard P.
- NEBRASKA
- OMAHA
Gifford, Harold
Judd, John H.
Lipp, Frank E.
Morrison, W. Howard
Rasgorsbek, Robert H.
Stokes, Wm. H.
Swab, Charles M.
Truhlsen, Stanley M.
- NEVADA
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Magee, George R.
- NEW HAMPSHIRE
- BERLIN
Ingalls, Raymond G.
- HANOVER
Ames, Adelbert, Jr.
Auten, Hanford L.
- NEW JERSEY
- ASBURY PARK
Fisher, James A.
- ATLANTIC CITY
Diskan, Samuel M.
Harley, Halvor L.
Harley, Robison D.
Weintrob, Joseph R.
- CAMDEN
Meyer, George P.
- EAST ORANGE
Cregar, John S.
- HACKENSACK
Speigelglass, A. B.
- MILLBURN
Fonda, G. E.
- NEWARK
Rosen, Emanuel P.
Sherman, A. Russell
Sherman, Elbert S.
- PASSAIC
Ehrenfeld, Edward
Lang, Richard E.
- PRINCETON
Abrams, Henry
- SOUTH PLAINFIELD
Levy, Abram
- SUMMIT
McAtpine, Paul T.
- TEANECK
Berry, A. Erwin
- TRENTON
Sacks-Wilner, Erwin
Sharbaugh, George B.
Wilner, Arthur S.
- VERONA
D'Amico, Thomas V.
- NEW MEXICO
- ALBUQUERQUE
Dillalunt, Jack A.
Schonberg, Albert L.
- LOS ALAMOS
Goff, John L.
- NEW YORK
- ALBANY
Bedell, Arthur J.
- BINGHAMTON
Walling, Harry G.
- BROOKLYN
Cholst, Mortimer
Dolphin, Joseph M.
Evans, John N.
Fink, Austin I.
Lloyd, Ralph I.
Mandelbaum, Joseph
Ohly, John H.
Ralph, Fenn T.
Rosenberg, Abner S.
Rosenthal, Benj. C.
- BUFFALO
Addington, Charles H.
Brennan, James W.
Freeman, Sheldon B.
Koenig, Ivan J.
LeWin, Thurber
Luhr, John P.
Reitz, Herbert R.
- FOREST HILLS, L.I.
Simonton, John T.
- FREEPORT, L.I.
Troncoso, Manuel U.
- GLEN COVE, L.I.
Boyd, James L.
- JAMESTOWN
Franks, Myron B.
- LONG ISLAND CITY
Shapiro, Ernest K.
- NEW YORK
Bassen, Edward J.
Berens, Conrad
Bloodfield, Sylvan
Boyes, Truman L.
Breinin, Goodwin M.
Bronk, Henry N.
Carter, George Z.
Castroviejo, Ramon
Chace, Robert R.
Constantine, F. H.
Curtin, Brian J. H.
Day, Robert M.
DeVoe, Arthur G.
Dische, Zacharias
Doherty, Wm. R.
Dunnington, John H.
Emerson, George O., Jr.
Esterman, Benjamin
Flynn, John E.
Foote, Franklin M.
Friedman, Benjamin
Givner, Isadore
Gordon, Dan M.
Guy, Loren P.
Hardy, LeGrand H.
Hartshorne, Isaac
Hill, John M.
Horwich, Harry
Imus, Henry A.
Kahan, Edmund
Katzin, Herbert M.
Kirby, Daniel B.
Knapp, Arthur A.
Knighton, Willis S.
Koch, F. L. P.
Kornzweig, Abraham L.
Kronenberg, Bernard
Krug, Joseph H.
Lang, Louis R.
Last, Murray A.
Laval, Joseph
McLean, John M.
Macnic, John P.
Marcus, Arthur A.
Merriam, George R., Jr.
- Minsky, Henry
Paton, R. Townley
Payne, Brittain F.
Pecera, Charles A.
Posner, Adolph
Reese, Algernon B.
Reid, John I., Jr.
de Roeth, Andrew, Jr.
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Saltzman, Samuel L.
Samuels, Bernard
Sauer, John J.
Schachat, Walter S.
Schlossman, Abraham
Sitchevska, Olga
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Smith, James W.
Theodore, Frederick H.
Tusak, Ervin A.
von Sallmann, Ludwig
Webster, David H.
Wheeler, Maynard G.
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Seigel, Edward
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Norton, Herman J., Jr.
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PENNSYLVANIA

ARDMORE

Vogel, Adolph W.

BEDMINSTER

Duane, Thomas D.

BELLEFONTE

Covey, John K.

BERWICK

Ross, Joseph V. M.

BRYN MAWR

McGavic, John S.

CHESTER

Cross, George H.

DANVILLE

Jacobs, Clyde H.

ERIE

Alberstadt, Norbert F.

HARRISBURG

Martz, George E.

LANCASTER

Smith, E. Gerard

MORRISTOWN

Tait, Edwin F.

PHILADELPHIA

Adler, Francis H.
Blazar, Howard A.
Brav, Solomon S.
Cowan, Alfred
DeLong, Samuel L.
Gowens, Harry L., Jr.
Hallett, Joseph W.
Krewson, Wm. E., III
Leopold, Irving H.
Lutman, Frank C.
McDonald, P. Robb
Mullen, Carroll R.
Reese, Warren S.
Scheie, Harold G.
Shannon, C. E. G.
Spaeth, Edmund G.
Tassman, Isaac C.
Trueman, Robert H.
Waldman, Joseph
Zentmayer, Wm.

PITTSBURGH

Billings, Robert J.
Davies, Robert H.
Goldberg, Sol
Linn, Jay G., Jr.
Linn, Jay G., Sr.
Novak, Joseph F.
Plumer, John S.
Steinberg, Abraham
Thorpe, Harvey E.
Weisser, Charles W.

READING

Craig, Paul C.

SHARON

Riddle, Ransford J.
Snyder, M. Wilson

SUMMIT HILL

Bonner, Wm. R.

TOWANDA

Redding, Willis A.

WARREN

Anderson, Edwin R.

WASHINGTON

McMurray, John B.

RHODE ISLAND

NEWPORT

Mills, Dawson A.

TENNESSEE

MEMPHIS

Lewis, Phillip M.
Rychener, Ralph O.

NASHVILLE

Zerfoss, Kate S.

TEXAS

AMARILLO

Jacobson, Jerry H.
Streit, August J.

AUSTIN

Hilgartner, H. L.
Key, Samuel N., Jr.
Legett, Carey, Jr.

CORPUS CHRISTI

Gill, Earl K.

DALLAS

Cary, Edward H.
Meisenbach, Albert E., Jr.
Thomas, Maxwell

EL PASO

Caylor, Robert N.
Schuster, Stephen A.

FORT HOOD

Chambers, Arthur L., II

GALVESTON

Potter, Wm. B.

HOUSTON

Elles, Norma B.
Goar, Everett L.
Griffey, Edward W.
Schultz, Jacob F.
Vanzant, Thomas J.

MCALLEN

Frink, Berton F.

PORT ARTHUR

Heare, Louis C.

RANDOLPH FIELD

Byrnes, Victor A.

SAN ANTONIO

Matthews, John L.
Mims, James L., Jr.

TEMPLE

McKay, Edward D.
Veirs, Everett R.

UTAH

PROVO

Oaks, Lewis W.

SALT LAKE CITY

Smith, Homer E.

VIRGINIA			MILWAUKEE			BRITISH COLUMBIA		
PORTSMOUTH			Blankstein, Samuel S.			VANCOUVER		
Nadbach, Rudolph P.			Haessler, F. H.			Mallek, Howard		
RICHMOND			RACINE			Minnes, James F.		
Courtney, R. H.			Kadin, Maurice			CENTRAL AND LATIN AMERICA		
Guerry, duPont III			HAWAII			BRAZIL		
Sheppard, L. Benjamin			HONOLULU			BAHIA		
Wortham, Edwin IV			Holmes, Wm. J.			de Andrade, Cesario		
ROANOKE			Pang, Herbert G.			MISAS GERAIS		
Young, Charles A.			PUERTO RICO			Dasilva, Antonio I.		
Young, Charles A. Jr.			PUERTE DE TIERRA			SAO PAULO		
WINCHESTER			Carrasquillo, Honorio F.			Alvaro, Moacyr E.		
McGuire, H. H.			SANTURCE			CUBA		
McGuire, Wm. P.			Buxeda, Roberto			HAVANA		
WASHINGTON			CANADA			Ferrer, Horatio		
BREMERTON			ALBERTA			PERU		
Benson, Clifton E.			EDMONTON			LIMA		
LONGVIEW			Duggan, J. Winston			Barrer, Luciano E.		
Hill, Robert V.			Marshall, M. R.			Raffo, Julio C.		
SEATTLE			MANITOBA			PHILLIPINE ISLANDS		
Drell, Maurice J.			WINNIPEG			MANILA		
Hanson, A. George			Elvin, Norman L.			De Ocampo, Geminiano		
Jensen, Carl D. F.			ONTARIO			Velarde, Herminio Sr.		
SPOKANE			LONDON			ENGLAND		
Buesseler, John A.			Dyson, Charles			LONDON		
de Roeth, Andrew F. M.			TORONTO			Duke-Elder, Lady Phyllis		
VANCOUVER			Elliot, Alfred J.			Duke-Elder, Sir Stewart		
Dunnavan, Floyd L.			Hawks, Gordon H.			SWITZERLAND		
WALLA WALLA			McCulloch, Clement			GENEVA		
Stevens, Ralph W.			MacDonald, Alexander			Blum, John		
WENATCHEE			MacDonald, Roy K.			TURKEY		
Miller, Claude K.			Ormsby, Hugh L.			ISTANBUL		
Radewan, Milton G.			Shusterman, Morris			Sezer, F. Necolet		
WEST VIRGINIA			QUEBEC			BRITISH WEST INDIES		
CLARKSBURG			MONTREAL			TRINIDAD		
Thomas, Harry V.			Brault, Jules			MARAVAI		
HUNTINGTON			Cloutier, Roland			Chan-Pong, Norman R.		
Esposito, Albert C. M.			Locke, John C.					
Polan, Charles M.			Viger, R. J.					
WISCONSIN			QUEBEC CITY					
CAMP MCCOY			Pichette, Henri					
McClure, G. David								

NEW MEMBERS

1952

Anderson, Banks	DeShan, Samuel M.	Horwich, Harry	Rothen, Robert M.
Ballintine, E. J.	Dolphin, J. M.	Hurwitz, Paul	Rouse, David M.
Bergmann, R. B.	Dwiggins, Horace G.	Kronenberg, Bernard	Sacks-Wilner, Erwin
Blankstein, Samuel S.	Dunphy, Edwin B.	Lang, R. E.	Schlossmann, Abraham
Bray, Solomon S.	Esposito, A. C. M.	Legett, Carey	Snydacker, Daniel
Breinin, G. M.	Esterman, Benjamin	Lyda, Wood	Van Heuven, J. A.
Buxeda, Roberto	Fitzgerald, J. R.	McClure, G. D.	Veira, Everett R.
Carter, G. Z.	Flynn, G. E.	Mallek, Howard	Vogel, A. W.
Christiansen, Gordon S.	Forrest, R. L.	Marcus, A. A.	Waugh, Richey L., Jr.
Cowan, Alfred	Gowers, Harry L., Jr.	Marg, Elwin	Wilder, H. C.
Davies, R. H.	Haik, George M.	Monahan, R. H.	Wiley, G. A.
de Francois, Walter	Hart, Clinton E.	O'Brien, J. M.	Wyman, G. J.
de Suto-Nagy, I. K.	Hebbard, F. W.	Posner, Adolph	Young, C. A., Jr.

